UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

Date: August 5, 2014

Subject: **Flupyradifurone: Human Health Risk Assessment for the First Food Use on:** Root Vegetables Except Sugar Beet (Subgroup 1B), Tuberous and Corm Vegetables (Subgroup 1C), Bulb Vegetables (Group 3-07), Leafy Vegetables (Except Brassica) (Group 4), Taro Leaves, Turnip Tops, Head and Stem Brassica Vegetables (Subgroup 5A), Leafy Brassica Greens Vegetables (Subgroup 5B), Edible-Podded Legume Vegetables (Subgroup 6A), Succulent Shelled Pea and Bean (Subgroup 6B), Died Shelled Pea and Bean (except Soybean) (Subgroup 6C), Foliage of Legume Vegetables (except Soybean) (Subgroup 7A), Soybean (Seed), Fruiting Vegetables Except Cucurbits (Group 8-10), Cucurbit Vegetables (Group 9), Citrus Fruits (Group 10-10), Pome Fruits (Group 11-10), Bushberry (Subgroup 13-07B) except Cranberry, Small Fruit Vine Climbing (Except Fuzzy Kiwifruit) (Subgroup 13-07F), Low Growing Berry (Subgroup 13-07G) except Cranberry, Tree Nuts (Group 14-12), Cereal Grains Except Rice (Crop Group 15, Except Rice), Forage, Fodder and Straw of Cereal Grains (Crop Group 16), Nongrass Animal Feeds (Forage, Fodder, Straw and Hay) (Group 18), Cottonseed (Subgroup 20C), Coffee, Hops, Peanuts, Prickly Pear Cactus, and Pitaya.

PC Code: 122304
Decision No.: 471642
Petition No.: 2F8101
Risk Assessment Type: Aggregate Risk Assessment
TXR No.: NA
MRID No.: NA

DP Barcode: D407063
Registration Nos.: 264-RRUE, 264-RURR
Regulatory Action:
Case No.: N A
CAS No.: 951659-40-8
40 CFR: NA

FROM: Kristin Rury, Biologist
Steve Funk, Senior Chemist
Meheret Negussie, Chemist
Whang Phang, Senior Toxicologist
Vincent Chen, Toxicologist
Risk Assessment Branch III
Health Effects Division (7509P)

THROUGH: Christine Olinger, Branch Chief
Risk Assessment Branch III
Health Effects Division (7509P)

TO: Jessica Rogala, Risk Manager Reviewer
Insecticide Branch
Registration Division (7505P)

Table of Contents

1.0 Executive Summary

Flupyradifurone (BYI 02960) is a new butenolide insecticide currently undergoing global joint review (GJR) with Australia, Brazil, Canada, and Mexico. Butenolide insecticides, like nicotine and neonicotinoid insecticides, bind to nicotinic acetylcholine receptors (nAchR). Once the flupyradifurone binds to the receptor, the receptor is blocked causing insect death.

Proposed Use Profile
Bayer CropScience has proposed one technical and two end-use product (EP) registrations: Sivanto™ (EPA Reg. No. 264-RRUR) and BYI 02960 480 FS (EPA Reg. No. 264-RRUE).

Sivanto™ may be applied at single application rates ranging from 7.0 – 28 fl oz/A (0.091 – 0.365 lb ai/A), with a maximum seasonal application rate of 0.365 lb ai/A to the numerous proposed agricultural crops via ground, aerial, or chemigation equipment. The proposed Sivanto™ label requires occupational handlers to wear the following personal protective equipment (PPE): long sleeved shirts, long pants, shoes, socks, and chemical resistant gloves. The proposed restricted entry interval (REI) is four hours.

BYI 02960 480 FS may be applied as a single seed treatment application at a rate of 0.045 – 0.068 mg ai/seed (0.00036 - 0.00054 lb ai/lb seed). The soybean seeds are treated with standard slurry or mist commercial seed treatment equipment. The proposed seed treatment label requires seed treaters and workers cleaning the treatment facilities to wear the following PPE: long sleeved shirts, long pants, shoes, socks, and chemical resistant gloves. Baggers and others involved in the packaging of treated seed are required to wear long sleeved shirts, long pants, shoes, and socks.

There are no proposed residential uses of flupyradifurone.

Exposure Profile
There is potential for occupational short- and intermediate-term dermal and inhalation exposure to flupyradifurone during mixing, loading, applying, and post-application activities. There is also potential for acute and chronic exposure through food and drinking water from the proposed uses of flupyradifurone.

Toxicity/Hazard
The most sensitive effects seen in the flupyradifurone database were skeletal muscle atrophy/degeneration in dogs. With repeated dosing, reductions in body weight and food consumption were commonly seen in various studies and in all species of test animals (rats, mice, dogs, and rabbits). The liver and thyroid were shown to be the common findings of flupyradifurone toxicity. The database appears to suggest that dogs are more sensitive to the effects of flupyradifurone; however, with body weight adjustments (based on a ¾ scaling factor – shown in Appendix A.5), the dog and rat are almost equally as sensitive in response to flupyradifurone toxicity. The skeletal muscle atrophy/degeneration seen in the 90-day and one-year dog studies formed the basis for chronic dietary exposure and short- and intermediate-term occupational toxicity endpoints. The points of departure (PODs) were 7.8 mg/kg/day and 12 mg/kg/day for chronic dietary exposure and for short- and intermediate-term occupational

exposure assessments, respectively. The developmental toxicity study in rats demonstrated no evidence of susceptibility in developing animals. In the rabbit developmental toxicity study, there was an increase in the incidence of fetal death at 80 mg/kg/day (the highest dose tested), a dose that did not produce adverse effects in the maternal animals. Therefore, a quantitative increase in susceptibility was demonstrated in the rabbit developmental toxicity study. In the 2-generation reproduction study in rats, decreased parental body weights ($\geq$ 10%) were seen at the LOAEL of 137 mg/kg/day (parental NOAEL = 37.8 mg/kg/day). In contrast, body weight decreases that were considered adverse were seen in F_2 pups at 37.8 mg/kg/day (the parental NOAEL and the offspring LOAEL; offspring NOAEL = 7.7 mg/kg/day). These findings suggest quantitative susceptibility for developing young animals. Although flupyradifurone produced quantitative susceptibility in rabbit developmental toxicity study and qualitative susceptibility in the rat reproductive toxicity study, the PODs selected for risk assessment are protective of the effects seen in the developing fetuses and young animals. Therefore, there are no concerns for reproductive or developmental toxicity of flupyradifurone, and no concerns for increased susceptibility to the developing young. HED presently has sufficient information to evaluate the hazards associated with exposure to flupyradifurone at this time and the Food Quality Protection Act (FQPA) safety factor has been reduced to 1X. Flupyradifurone also produced clinical signs (piloerection and pupillary dilatation) indicative of neurotoxicity in the acute neurotoxicity study, and these clinical signs were used to establish the toxicity endpoint with a point of departure of 35 mg/kg for acute dietary exposure assessment. The exposure databases are complete or are estimated based on data that reasonably account for potential exposures.

Flupyradifurone is classified as “not likely to be carcinogenic to humans.” Flupyradifurone exhibits low acute mammalian toxicity via oral, dermal, and inhalation routes of exposure (Category III or IV for acute lethality and irritation studies) and is not a dermal irritant or sensitizer. HED waived the requirement for the subchronic inhalation toxicity study (TXR#0056903).

Dietary Exposure (Food and Water) and Risk Estimates
Unrefined acute and chronic dietary analyses were conducted for flupyradifurone; the assessments incorporated recommended tolerance-level residues and default or empirical processing factors, conservative drinking water estimates, and assumed that 100% of the proposed crops were treated. The results of the acute and chronic analyses do not exceed the Agency’s level of concern (LOC) for the general U.S. population and all population subgroups. At the 95th percentile of exposure, the acute dietary (food and drinking water) risk estimates utilized 24% of the acute population adjust dose (aPAD) for the general U.S. population and utilized 38% of the aPAD for children 1-2 years old, the most highly exposed population subgroup. The chronic dietary (food and drinking water) risk estimates utilized 39% of the chronic population adjusted dose (cPAD) for the general U.S. population and utilized 84% of the cPAD for children 1-2 years old, the most highly exposed population subgroup.

Studies submitted in support of the registration of flupyradifurone indicate that there could be exposure to difluoroacetic acid (DFA) in drinking water and in food (plants and animals). DFA was shown to be a mammalian metabolite with approximately 6% of flupyradifurone administered to rats being converted to DFA, and DFA was a metabolite in the ruminant and poultry metabolism studies. The most sensitive toxic effects to be used in the risk assessment for flupyradifurone would not be expected from DFA, which has a very different chemical structure. A range-finding and subchronic toxicity study with DFA showed a similar potency to but different toxic effects (black foci in the glandular part of the stomach) than the parent compound (skeletal muscle atrophy and degeneration in dogs, and decreased body weight and food consumption in rats, mice, dogs, and rabbits), indicating that risk from DFA should be assessed separately from the parent.

The Agency conducted a conservative screening-level chronic dietary exposure evaluation to estimate risks from DFA. This evaluation assumed conservative drinking water concentrations, that 100% of the crops contained DFA at median residue values. The screening exposure evaluation of DFA showed 5-7X less exposure to DFA than to flupyradifurone. Therefore, since there is similar potency (albeit with different toxic effects) between flupyradifurone and DFA but less exposure expected to DFA than flupyradifurone, the Agency has no additional risk concerns about exposure to DFA.

Aggregate Exposure Risk Estimates
The only relevant aggregate risk assessments for flupyradifurone include acute and chronic exposure to residues in food and drinking water. The acute and chronic dietary risk assessments for the U.S. population and all population subgroups do not exceed the Agency's LOC (<100% PAD), as described above.

Occupational Risk
A short- and intermediate-term occupational risk assessment was performed for flupyradifurone use on the proposed crops and for the proposed seed treatment use. The LOC for occupational handler and post-application risk is a margin of exposure (MOE) < 100. There are no occupational handler risk estimates of concern for the proposed uses of flupyradifurone assuming baseline clothing (i.e., no PPE); for the agricultural uses of flupyradifurone, the short- and intermediate-term combined (dermal + inhalation) occupational handler MOEs ranged from 260 to 95,000. With the addition of gloves, as required on the flupyradifurone label, the short- and intermediate-term combined (dermal + inhalation) occupational handler MOEs ranged from 800 to 95,000. For the proposed seed treatment use of flupyradifurone, the combined (dermal + inhalation) short- and intermediate-term MOEs ranged from 2,000 to 14,000.

The occupational short-term post-application risk estimates resulted in dermal MOEs of >170 on the day of application and were not of concern. Based on the Agency's current practices, a quantitative non-cancer occupational post-application inhalation exposure assessment was not performed for flupyradifurone at this time. If new policies or procedures are put into place, the Agency may revisit the need for a quantitative occupational post-application inhalation exposure assessment for flupyradifurone.

Review of Human Research
This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These data, which include studies from Pesticide Handlers Exposure Database (PHED 1.1); the Agricultural Handlers Exposure Task Force (AHETF) database; ExpoSAC Policy 14, 15.1 (SOPs for Seed Treatment) and The Reviewer's Aid to Calculating Occupational Exposure From Activities Related to Agricultural

Seed Treatment; and the Agricultural Reentry Task Force (ARTF) database; are (1) subject to ethics review pursuant to 40 CFR 26, (2) have received that review, and (3) are compliant with applicable ethics requirements. For certain studies, the ethics review may have included review by the Human Studies Review Board. For citations of these data, see Appendix D.

Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," http://www.eh.doe.gov/oepa/guidance/justice/eo12898.pdf).

2.0 HED Recommendations

Provided revised petition Sections B and F are submitted, there are no deficiencies that would preclude granting a Section 3 registration on the proposed crops. The specific tolerance recommendations are detailed in Section 2.2.2, and revisions to petitioned-for tolerances are discussed in Section 2.2.3.

2.1 Data Deficiencies

Guideline 875.2100 – Dislodgeable Foliar Residue Data

Since the highest estimated occupational post-application exposure using default dislodgeable foliar residue (DFR) values is not minimal in comparison to the level of concern (i.e., the calculated MOE is not greater than 2 times higher than the level of concern, MOE = 170 compared to the LOC of 100); therefore, EPA is requiring the 40CFR DFR data requirement to facilitate any necessary exposure assessments refinements and to further EPA’s general understanding of the availability of dislodgeable foliar pesticide residues.

2.2 Tolerance Considerations

2.2.1 Enforcement Analytical Method

Only parent flupyradifurone is considered a residue of concern for tolerance enforcement of plants and livestock commodities.

An adequate analytical method (Method RV-001-P10-03) which uses high performance liquid chromatography with tandem mass spectrometry (HPLC/MS-MS) to quantitate residues of flupyradifurone in various crops is available for enforcement. The validated limit of quantification (LOQ) is 0.01 mg/kg for flupyradifurone in most commodities.

An HPLC/MS/MS method, Method RV-004-A11-05 (latest revision of the data collection method RV-004-A11-04), is adequate as the enforcement method for determination of residues of flupyradifurone in livestock commodities The validated LOQ for flupyradifurone is 0.01 mg/kg in all matrices

FDA multiresidue methods (MRMs) are suitable for flupyradifurone only in non-fatty matrices. The methods are not suitable for fatty matrices or matrices that require further clean-up.

2.2.2 Recommended Tolerances

HED has reviewed the available residue data and has determined the appropriate tolerance levels for residues of flupyradifurone (Table 2.2.2). The recommended tolerance expression is as follows:

Tolerances are established for residues of the insecticide flupyradifurone, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only flupyradifurone, 4-[[(6-chloro-3-pyridinyl)methyl](2,2-difluoroethyl)amino]- 2(5H)-furanone.

Table 2.2.2. Tolerance Summary for Flupyradifurone

Commodity	**Proposed Tolerance (ppm)**	**HED-Recommended Tolerance (ppm)**	***Comments (correct commodity definition)***
Aspirated grains fractions	40	40	Grain, aspirated grain fractions
Root vegetables except sugar beets (Crop Subgroup 1B)	1.5	0.9	*Vegetable, root, except sugar beet, subgroup 1B*
Tuberous and corm vegetables (Crop Sub-Group 1C)	0.5	0.05	Vegetable, tuberous and corm, subgroup 1C
Crop subgroup 3-07A, onion, bulb, subgroup	0.3	0.09	Onion, bulb, subgroup 3-07A
Crop subgroup 3-07B, onion, green, subgroup	3	3.0	Onion, green, subgroup 3-07B
Leafy vegetable, except Brassica vegetables (Crop Group 4)	40	none	*Subgroup tolerances will be recommended.*
Leafy greens, subgroup 4A	-	30	*The residue range among the representative crops exceeds the suggested 5X (6 – 7 X), but use of the highest representative crop (spinach) tolerance estimate is protective.*
Leaf petioles, subgroup 4B	-	9.0	
Taro, leaves	40	30	*Translation from subgroup 4A.*
Head and Stem Brassica (Crop Subgroup 5A)	6	6.0	*Brassica*, head and stem, subgroup 5A
Leafy Brassica Greens (Crop Subgroup 5B)	40	40	*Brassica*, leafy greens, subgroup 5B
Turnip greens	40	40	Translation from leafy *Brassica* greens

Table 2.2.2. Tolerance Summary for Flupyradifurone			
Commodity	**Proposed Tolerance (ppm)**	**HED-Recommended Tolerance (ppm)**	***Comments (correct commodity definition)***
Edible-podded legume vegetables (Crop Subgroup 6A)	5	3.0	Vegetable, legume, edible podded, subgroup 6A
Succulent, Shelled Pea and Bean (Crop Subgroup 6B)	4	None	*The residue range between the representative crops exceeds the suggested 5X by a substantial amount, 13X. Crop-specific tolerances (pea, bean) are listed below.*
Pea, succulent	-	2.0	See 40CFR§180.1
Bean, succulent	-	0.2	See 40CFR§180.1
Dried, shelled pea and bean (except soybean) (crop subgroups 6c)	6	3.0	Pea and bean, dried shelled, except soybean, subgroup 6C
Foliage of legume vegetables, including soybeans (Crop Group 7, forage, green vines)	40	30	Vegetable, foliage of legume, group 7
Foliage of legume vegetables, including soybeans (Crop Group 7), Hay	50	None	*Only one tolerance is possible per crop group. The recommended 30 ppm covers vines, forage, and hay from pea, bean, and soybean.*
Soybean, seed	4	1.5	
Fruiting vegetables, except cucurbits (Crop Group 8-10), fruit	3	1.5	Vegetable, fruiting, group 8-10
Tomato, paste	4	None	*Covered by the fruiting vegetable group tolerance.*
Cucurbit vegetables (Crop Group 9), fruit	2	0.40	Vegetable, cucurbit, group 9
Citrus fruits (Crop Group 10-10), fruit	3	3.0	Fruit, citrus, group 10-10
Citrus, pulp, dried	15	10	Fruit, Citrus, dried pulp *Orange HAFT X P_f = 4.6 ppm X 1.77 = 8.14 ppm*
Pome fruits (Crop Group 11-10), fruit	1.5	0.70	Fruit, pome, group 11-10
Bushberry group (Crop Subgroup 13-07B), except cranberry	4	4.0	Bushberry, except cranberry, subgroup 13-07B
Small fruit vine climbing subgroup, except fuzzy kiwifruit (Crop Subgroup 13-07F)	3	3.0	Fruit, small vine climbing, except fuzzy kiwifruit, subgroup 13-07F
Grapes, raisin	6	5.0	Grape, raisin Grape HAFT X P_f = 1.90 ppm X 2.5 = 4.75 ppm

Table 2.2.2. Tolerance Summary for Flupyradifurone

Commodity	Proposed Tolerance (ppm)	HED-Recommended Tolerance (ppm)	*Comments (correct commodity definition)*
Low growing berry subgroup (Crop Subgroup 13-07G), except cranberry	1.5	1.5	Berry, low growing, except cranberry, subgroup 13-07G
Tree nuts (Crop Group 14), nutmeat	0.15	0.02	Nut, tree, group 14-12
Pistachio	0.15	None	*Pistachio is included in the tree nut group 14-12.*
Tree nuts (Crop Group 14), hulls	15	15	Almond, hulls
Grain, cereal, group 15, except rice; grain	4	3.0	Grain, cereal, group 15, except rice and corn
Pop corn, grain	-	0.05	Corn, pop, grain
Field corn, grain	-	0.05	Corn, field, grain
Sweet corn, kernels plus cobs with husks removed (K+CWHR)	0.4	0.05	Corn, sweet, kernel plus cob with husks removed
Wheat, bran	5	None	*Wheat bran is covered by the cereal grain group 15 tolerance.*
Rice, grain (rotational crop)	4	None	*No supporting data.*
Grain, cereal, forage, fodder and straw, Group 16, forage	20	30	Grain, cereal, forage, fodder and straw, group 16
Grain, cereal, forage, fodder and straw, Group 16, hay	40	None	*Only one tolerance is possible per crop group. The recommended 30 ppm covers hay, forage, fodder, straw, and stover of all cereal grains. The proposed 40 ppm for hay included residues from DFA, not part of the recommended definition.*
Grain, cereal, forage, fodder and straw, Group 16, straw	30	None	
Grain, cereal, forage, fodder and straw, Group 16, stover	15	None	
Cotton, undelinted seed, Crop Subgroup 20C	0.9	0.80	Cottonseed subgroup 20C
Cotton, gin by-products	40	40	Cotton, gin byproducts
Nongrass animal feeds, forage, Crop Group 18	20	None	*Inadequate number of trials for the representative commodity clover. Separate tolerances for clover with regional registration and alfalfa are listed elsewhere in this table.*
Alfalfa, forage	-	9.0	
Alfalfa, hay	-	20	
Nongrass animal feeds, hay, crop group 18	40	None	*Inadequate number of trials for the representative commodity clover. Separate tolerances for clover with regional registration and alfalfa are listed elsewhere in this table.*

Table 2.2.2. Tolerance Summary for Flupyradifurone			
Commodity	**Proposed Tolerance (ppm)**	**HED-Recommended Tolerance (ppm)**	***Comments (correct commodity definition)***
Coffee, bean, green[1]	2	1.5	Coffee, green bean
Coffee, bean, roasted; instant	3	None	*Covered by the coffee bean tolerance.*
Hops	20	10	Hop, dried cones
Peanut, hay	30	20	
Peanut, nutmeat	0.15	0.04	Peanut
Prickly pear cactus, fruit	0.5	0.30	Cactus, fruit
Pitaya, fruit	0.5	0.30	Pitaya *Translation from prickly pear cactus fruit.*
Prickly pear cactus, pads	0.9	0.70	Cactus, pads
Cattle, fat	0.2	0.20	
Cattle, meat	0.2	0.30	
Cattle, meat byproducts	0.7	1.0	
Goat, fat	0.2	0.20	
Goat, meat	0.2	0.30	
Goat, meat byproducts	0.7	1.0	
Hog, fat	0.2	0.01	
Hog, meat	0.2	0.01	
Hog, meat byproducts	0.7	0.04	
Horse, fat	0.2	0.20	
Horse, meat	0.2	0.30	
Horse, meat byproducts	0.7	1.0	
Milk	0.3	0.15	
Poultry, eggs	0.3	0.01	Egg
Poultry, meat	0.4	None	*No reasonable expectation of residues*
Poultry, meat byproducts	0.5	None	*No reasonable expectation of residues*
Sheep, fat	0.2	0.20	
Sheep, meat	0.2	0.30	
Sheep, meat byproducts	0.7	1.0	
Tolerance with Regional Registration			
Clover, forage	-	20	*Use limited to Oregon, Idaho, Washington*
Clover, hay	-	30	*Use limited to Oregon, Idaho, Washington*

[1] There is no US registration.

2.2.3 Revisions to Petitioned-For Tolerances

The Petitioner requested a definition for enforcement of tolerance as the sum of flupyradifurone and difluoro acetic acid (DFA) and 4-[(2,2-difluoroethyl)amino]furan-2(5*H*)-one (DFEAF), expressed as flupyradifurone, which significantly inflated the field trial residue values and resulted in higher tolerance values. EPA, consistent with its global review partners, has selected parent flupyradifurone only as the residue definition for tolerance enforcement. Flupyradifurone is the major portion of the residue in plant commodities and in some livestock commodities. In other livestock commodities, it is present at the same approximate concentration as some metabolites. Moreover, the significant metabolite difluoroacetic acid (DFA) is not suitable for enforcement purposes, as its concentration is erratic with time. The harmonized enforcement definition, flupyradifurone only, will facilitate trade and is predicted to be the residue definition adopted by Codex in the future based on application of their policy. Therefore, EPA is reducing the tolerance values for the petitioned-for tolerances for the following commodity groups/subgroups or commodities: cattle, goat, hog, horse, and sheep meat and meat byproducts; hog fat; milk; poultry eggs; root vegetables subgroup 1B; tuberous and corm vegetables subgroup 1C; bulb onion subgroup 3-07A; leafy vegetable group 4; legume vegetables subgroup 6A,6B,6C; soybean; foliage of legume vegetables group 7; fruiting vegetables group 8-10; cucurbit vegetables group 9; citrus pulp; pome fruits group 11-10; grape raisins; bushberry subgroup 13B except lowbush blueberry; tree nut group 14; cereal grain group 15 except rice and except corn; sweet corn, cereal grain forage, fodder, and straw group 16; nongrass animal feeds crop group 18; cotton undelinted seed; coffee bean; hops; peanut hay; peanut; prickly pear cactus fruit and pad.

The petition requested a tolerance for root vegetables, except sugar beets subgroup 1B at 1.5 ppm. The ratio of highest average field trials (HAFTs) of the representative commodities (carrot/radish, 0.603/0.046 ppm) was 13, but the ratio of the median residue value was 1.8. The small median ratio indicates that the central tendency of both carrot and radish residue values are similar and that a single tolerance would be appropriate for the subgroup, represented by carrot and radish. The higher tolerance estimate from carrot (0.90 ppm) will cover all members of the subgroup.

The petition requested a tolerance for the leafy vegetable, except brassica vegetables, group 4 at 40 ppm. Based on the available residue data, EPA is establishing separate tolerances for each of the subgroups of group 4, instead of a single tolerance for the whole group. For subgroup 4A (leafy greens), EPA is establishing a tolerance at 30 ppm, based on the highest residues, which were found on the representative crop spinach. For subgroup 4B (leafy petioles), EPA is establishing a separate tolerance at 9.0 ppm based on the celery residues. The leafy greens subgroup tolerance was translated to cover taro leaves; therefore, EPA is establishing a tolerance for taro leaves at 30 ppm, rather than the 40 ppm requested.

The petitioned-for tolerance for the shelled pea and bean subgroup 6B at 4 ppm was not possible because the residues on the garden pea and lima bean were substantially different. Residues differ by more than 5X between succulent peas and succulent beans. In accordance with 40 CFR 180.40(g), a subgroup tolerance is not normally appropriate; rather, EPA may establish individual crop tolerances. Therefore, EPA is establishing individual tolerances for succulent peas and succulent beans.

The petition requested a tolerance for cereal grains, grain, group 15 except rice at 4 ppm. The residues on sweet corn and field corn grain were much lower than those on sorghum, wheat, and barley grains; therefore, EPA is excluding corn (field corn, popcorn, and sweet corn) grain from that group 15 tolerance, as well as rice. Based on available residue data, EPA is establishing separate tolerances for popcorn, grain, field corn, grain, and sweet corn (kernels plus cobs with husks removed) at 0.05 ppm. Under 180.40(h), EPA may exclude some commodities from a group tolerance where the residue levels are significantly higher or lower than the other commodities in the group. Corn, unlike the other cereal grains, has a protective husk and this difference is often reflected in lower residues for late season foliar applications. Therefore, EPA is excluding corn grain and rice from the crop group 15 tolerance and establishing separate tolerances for corn. The remaining cereal grains, represented by grain sorghum, barley, and wheat, are quite similar.

The petition requested a tolerance on nongrass animal feeds group 18, forage at 20 ppm and hay at 40 ppm. EPA is unable to establish group 18 tolerances at this time for forage and hay because data from only four field trials on clover (one of the representative crops) were available. Based on the available data, EPA is establishing tolerances for alfalfa and regional tolerances for clover (since use on clover is restricted to Washington, Oregon, and Idaho, the area where the field trials were conducted). A group tolerance could be considered if additional field trials for clover from diverse areas of the US were supplied.

The petition requested a tolerance for rice grain at 4 ppm as a rotational crop. EPA cannot establish this tolerance at this time because no data were provided to support this request. Rice field trial data are required to establish a tolerance.

The proposed wheat bran tolerance of 5 ppm is not necessary. The cereal grain group tolerance covers wheat bran. The highest average field trial (HAFT) residue for wheat grain was 0.73 ppm and the experimentally determined processing factor for the conversion of grain to bran was 2.4. Therefore, the tolerance estimate for wheat bran is 1.8 ppm (0.73 X 2.4). As 1.8 ppm is less than the 3 ppm cereal group tolerance, a separate tolerance for wheat bran is not needed.

EPA was petitioned for tolerances on tree nut group 14 and pistachio. In the Federal Register of August 22, 2012 (77 FR 50617) (FRL–9354–3), EPA issued a final rule that revised the crop grouping regulations. As part of this action, EPA expanded and revised the existing tree nut group 14. Changes to crop group 14 included adding the specialty commodities African nut tree, Brazilian pine, Bunya, Bur oak, Cajou nut, Candlenut, Coconut, Coquito nut, Dika nut, Ginkgo, Guiana chestnut, Heartnut, Japanese horse-chestnut, Mongongo nut, Monkey-pot, Monkey puzzle nut, Okari nut, Pachira nut, Peach palm nut, Pequi, Pili nut, Pine nut, Pistachio, Tropical almond and Yellowhorn including cultivars, varieties, and/or hybrids of these; and naming the new crop group tree nut group 14–12. EPA indicated in the August 22, 2012 final rule as well as the earlier November 9, 2011 proposed rule (76 FR 69693) (FRL–8887–8) that, for petitions for which a Notice of Filing had been published, the Agency would attempt to conform these petitions to the rule. Therefore, consistent with this rule, EPA has assessed exposure to the, insecticide flupyradifurone, assuming use under the revised tree nut group 14-12. Because revising the requested crop group to the updated crop group did not result in a risk of concern, EPA is establishing tolerances for flupyradifurone residues on tree nut group 14–12.

Cranberry was removed from subgroups 13-07B and 13-07G at the request of the petitioner as a modification to the original request.

Tolerances are not needed for the processed commodities tomato paste, roasted coffee, and instant coffee. The recommended tolerances for the raw agricultural commodities, tomato and green coffee bean cover the respective processed commodities. The highest average field trial (HAFT) result for coffee was 0.55 ppm, and the processing factors for roasted coffee and instant coffee were 0.59 and 1.9, respectively. Tolerance estimate (HAFT X processing factor; 0.55X0.59 = 0.32 ppm roasted bean; 0.55X1.9=1.0 ppm instant coffee) are less than the recommended green coffee bean tolerance (1.5 ppm). The HAFT for the tomato field trials was 0.57 ppm and the processing factor for conversion to paste was 2.0, and the product (0.57X2.0) is less than the recommended fruiting vegetable group tolerance (1.5 ppm).

Tolerances are not required for poultry meat and poultry meat byproducts, as the projected diet for poultry and the results of the poultry feeding study indicate that residues are not likely in poultry meat and poultry meat byproducts.

2.2.4 International Harmonization

Flupyradifurone has not been considered by the Codex system, and therefore there are no harmonization issues. The active global review participants, Australia, Canada, and the US, are working together to harmonize MRLs wherever possible. All plant commodity tolerances are harmonized. The livestock commodity tolerances for ruminant commodities are not harmonized with Canada, with US tolerance being approximately twice the corresponding Canadian tolerances. This is a direct result of the different diets (exposures) determined by Canada and the US. Canada does not consider forage and fodder crops that are not native to Canada. The US and Canada tolerances for eggs are harmonized. Canada will establish default tolerances for poultry meat and meat by-products at the LOQ. The US will establish no poultry tolerances as there is no reasonable expectation of residues. A comparison of specific tolerances/MRLs is provided in HED's summary of flupyradifurone residue data (S. Funk, 02/17/2014, D415670).

2.3 Label Recommendations

2.3.1 Recommendations from Residue Reviews

The proposed label pre-harvest interval (PHI) for prickly pear is 14 days, but the crop trials were conducted with a 21- day PHI. The label PHI must be changed to 21 days.

The proposed label specifies use on members of the non-grass animal feeds crop group 18 with use on clover limited to Washington, Idaho, and Oregon. However, clover and alfalfa are the representative commodities of this group, and there are an inadequate number of clover trials. Therefore, the label must be amended to allow use on alfalfa (nationally) and clover in Washington, Idaho, and Oregon. Uses on crop group 18 must be removed from the label.

A rotational crop interval of 30 days for rice is not adequately supported. The rotational field trials conducted in Europe at 50% of the seasonal rate shows no residues on barley grain at a 30 day PBI. However, the residue level at a 100% seasonal rate cannot be predicted. Since the use on rice is not supported by adequate rotational crop data and cereal grain primary trials cannot be used to establish a rice tolerance (see 2.2.3), rice falls under the crops not on the label and for which no tolerances exist; therefore, the appropriate interval is 12-months. The exception for rice must be removed from the label.

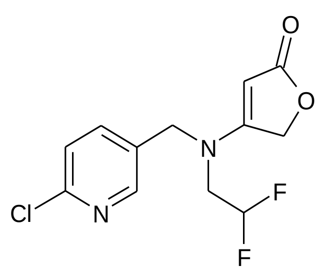
The label must be amended to indicate that uses in greenhouses are not allowed because supporting field trial studies for greenhouse uses were not submitted.

The proposed label specifies use on members of crop subgroup 1B (root vegetables). However, a crop subgroup tolerance could not be recommended. Therefore, the label must be amended to indicate use on carrot and radish only.

3.0 Introduction

Flupyradifurone is a member of the butenolide class of chemistry effective against a broad range of sucking insects. It has a similar insecticidal mode of action to neonicotinoids. Flupyradifurone is formulated into two systemic insecticide products: Sivanto 200 SL is for soil and foliar applications intended for the control of aphids, whiteflies, leafhoppers and other insects infesting many fruit, vegetable, plantation, row and specialty crops; and BYI 02960 480 FS is for soybean seed treatment. After uptake into the plant *via* the roots or translaminarly through leaf tissue, flupyradifurone is translocated acropetally in the xylem, in the direction of the transpiration stream and is distributed into plant cells.

3.1 Chemical Identity

Table 3.1. Flupyradifurone Nomenclature.	
Compound $C_{12}H_{11}ClF_2N_2O_2$	Chemical Structure 
Common name	Flupyradifurone
Company experimental name	BYI 02960
IUPAC name	4-[(6-chloro-3-pyridylmethyl)(2,2-difluoroethyl)amino]furan-2(5*H*)-one
CAS name	4-[[(6-chloro-3-pyridinyl)methyl](2,2-difluoroethyl)amino]- 2(5*H*)-furanone
CAS #	951659-40-8
End-use product/EP	Sivanto™ 200SL (1.67 lbs ai/gallon or 200 g ai/l soluble concentrate) BYI 02960 480 FS (4 lbs ai/gallon or 480 g ai/l flowable concentrate for seed treatment)

3.2 Physical/Chemical Characteristics

Flupyradifurone has substantial solubility in both organic solvents and water and a low octanol/water partition coefficient, and therefore is predicted to show no strong preference for fat versus muscle or for cream versus skim milk/whey. It has a low vapor pressure and not expected to volatilize.

3.3 Pesticide Use Pattern

Table 3.3.1. Proposed Use Pattern for Flupyradifurone					
Applic. Type	Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)	Use Directions and Limitations
BYI 02960 480 FS (4 lbs ai/gallon)					
Soybean					
Seed treatment	0.045 – 0.068 mg ai/seed, 30 – 45 g ai/100 kg, or 0.027[1]	1	0.365 (from uses, seed treatment and foliar)	N/A	Use only as a commercial water-based slurry. All seeds treated must be colored with an EPA-approved dye or colorant. Treated seeds must be labeled in accordance with the requirements of the Federal Seed Act.
Sivanto™ 200 SL (1.67 lbs ai/gallon)					
Cereal Grains (except rice)					
Foliar	0.183	-	0.365	7 sweet corn 7 forage 21 grain 21 straw 21 stover	Minimum retreatment interval 7 days. Minimum spray volume 10 gallons/acre for ground and 2 gallons/acre for aerial.
Cotton					
Foliar	0.183	-	0.365	14	Minimum retreatment interval 10 days. Minimum spray volume 10 gallons/acre for ground and 2 gallons/acre for aerial.
Non-Grass Animal Feeds (Crop Group 18 including alfalfa, clover, crown vetch, kudzu, lespedeza, lupin, milk vetch, sainfoin, trefoil, velvet bean, vetch)					
Foliar	0.183	-	0.365	7 forage, silage, hay, or seed of alfalfa, lespedeza, sainfoin 14 all other	Minimum retreatment interval 10 days. Minimum spray volume 10 gallons/acre for ground and 2 gallons/acre for aerial. Use on clover is limited to Idaho, Washington, and Oregon.
Peanut					
Foliar	0.183	-	0.365	7	Minimum retreatment interval 10 days. Minimum spray volume 10 gallons/acre for ground

Table 3.3.1. Proposed Use Pattern for Flupyradifurone					
Applic. Type	Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)	Use Directions and Limitations
					and 2 gallons/acre for aerial.
Root Vegetables (except sugar beet) (crop group 1B including garden beet, carrot, celeriac, chervil, chicory, ginseng, horseradish, parsley (turnip-rooted), radish, oriental radish, rutabaga, salsify, skirret, turnip)					
Foliar	0.183	-	0.365	7	Minimum retreatment interval 10 days. Minimum spray volume 10 gallons/acre for ground and 2 gallons/acre for aerial.
Tuberous and Corm Vegetables (crop group 1C including Arracacha, Arrowroot, Artichoke (Chinese and Jerusalem), Canna (edible), Cassava (bitter and sweet), Chayote (root), Chufa, Dasheen (taro), Ginger, Leren, Potato, Sweet potato, Tanier (cocoyam), Turmeric, Yam bean (jicama, manoic pea), Yam (true)					
Foliar	0.183	-	0.365	7	Minimum retreatment interval 7 days. Minimum spray volume 10 gallons/acre for ground and 2 gallons/acre for aerial.
Leafy Vegetables (except *Brassica*) (crop group 4 including Amaranth (leafy amaranth, Chinese spinach, tampala), Arugula (Roquette), Cardoon, Celery, Celtuce, Chervil, Chinese celery, Chrysanthemum (edible-leaved and garland), Corn salad, Cress (garden), Cress (upland, yellow rocket, winter cress), Dandelion, Dock (sorrel), Endive, Florence fennel (sweet anise, sweet fennel, Finocchio), Lettuce (head and leaf), Orach, Parsley, Purslane (garden and winter), Radicchio (red chicory), Rhubarb, Spinach [including New Zealand and vine (Malabar spinach, Indian spinach)], Swiss chard, Taro leaves					
Foliar	0.183	-	0.365	1	Minimum retreatment interval 7 days. Minimum spray volume 10 gallons/acre for ground and 2 gallons/acre for aerial.
***Brassica* (Cole) Leafy Vegetables** (crop group 5 including Broccoli, Broccoli Raab (*rapini*), Brussels sprouts, Cabbage, Cauliflower, Cavalo broccolo, Chinese broccoli (*gai lon*), Chinese cabbage (*bok choy*), Chinese cabbage (*napa*), Chinese mustard cabbage (*gai choy*), Collards, Kale, Kohlrabi, Mizuna, Mustard greens, Mustard spinach, Rape greens) and Turnip Greens					
Foliar	0.183	-	0.365	1	Minimum retreatment interval 7 days. Minimum spray volume 10 gallons/acre for ground and 2 gallons/acre for aerial.
Legume Vegetables (succulent or dried) (crop group 6 including Edible Podded and Succulent Shelled Pea and Bean and Dried Shelled Pea and Bean (*Lupinus* spp., including grain lupin, sweet lupin, white lupin, and white sweet lupin) Bean (*Phaseolus* spp., including field bean, kidney bean, lima bean, navy bean, pinto bean, runner bean, snap bean, tepary bean, wax bean) **Bean** (*Vigna* spp., including adzuki bean, asparagus bean, blackeyed pea, catjang, Chinese longbean, cowpea, Crowder pea, moth bean, mung bean, rice bean, Southern pea, urd bean, yardlong bean) Pea (*Pisum* spp. including dwarf pea, edible-pod pea, English pea, field pea, garden pea, green pea, snow pea, sugar snap pea) Other Beans and Peas (Broad bean (fava bean), Chickpea (garbanzo bean), Guar, Jackbean, Lablab bean (hyacinth bean), Lentil, Pigeon pea, soybean (immature seed), Sword bean, soybean)					

Table 3.3.1. Proposed Use Pattern for Flupyradifurone					
Applic. Type	Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)	Use Directions and Limitations
Foliar	0.183	-	0.365	7 forage 7 leaves 7 vines 7 pods 7 hay 7 seed (fresh or dry, except soybean) 21 dry soybean seed	Minimum retreatment interval 7 days. Minimum spray volume 10 gallons/acre for ground and 2 gallons/acre for aerial.
Fruiting Vegetables (crop group 8-10 including Cocona, Eggplant (including: African, Pea and Scarlet eggplants), Garden huckleberry, Goji berry, Groundcherry, Martynia, Naranjilla, Okra, Pepino, Pepper (including all peppers i.e. bell, non-bell, hot, sweet, etc.), Roselle, Sunberry, Tomatillo, Tomato (including: Bush, Currant, Tree) including cultivars, varieties and/or hybrids of these commodities)					
Foliar	0.183	-	0.365	1	Minimum retreatment interval 10 days. Minimum spray volume 10 gallons/acre for ground and 2 gallons/acre for aerial.
Soil	0.365	1		45	The following methods of application may be used: 1. chemigation into root-zone through low-pressure drip, trickle, micro-sprinkler or equivalent equipment; 2. injection below the eventual seed-line prior to planting. Place pesticide 3-4 inches below seed-line; 3. potting hole drench at transplanting; or 4. post-transplant drench following setting and covering.
Cucurbit Vegetables (crop group 8 including Chayote (fruit), Chinese waxgourd (Chinese preserving melon), Citron melon, Cucumber, Gherkin, Gourd (edible, includes hyotan, cucuzza, hechima, Chinese okra), *Momordica* spp. (includes balsam apple, balsam pear, bitter melon, Chinese cucumber), Muskmelon (hybrids and/or cultivars of *Cucumis melo* including true cantaloupe, cantaloupe, casaba, Crenshaw melon, golden pershaw melon, honeydew melon, honey balls, mango melon, Persian melon, pineapple melon, Santa Claus melon, snake melon), Pumpkin, Squash (includes summer squash types such as: crookneck squash, scallop squash, straightneck squash, vegetable marrow, zucchini, and winter squash types such as acorn squash, butternut squash, calabaza, cushaw, Hubbard squash, spaghetti squash), Watermelon (includes hybrids and/or varieties of *Citrullus lanatus*)					
Foliar	0.183	-	0.365	1	Minimum retreatment interval 7 days. Minimum spray volume 10 gallons/acre for ground

Table 3.3.1. Proposed Use Pattern for Flupyradifurone					
Applic. Type	Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)	Use Directions and Limitations
					and 2 gallons/acre for aerial.
Soil	0.365	1		21	The following methods of application may be used: 1. chemigation into root-zone through low-pressure drip, trickle, micro-sprinkler or equivalent equipment; 2. injection below the eventual seed-line prior to planting. Place pesticide 3-4 inches below seed-line; 3. potting hole drench at transplanting; or 4. post-transplant drench following setting and covering.
Hops					
Foliar	0.137	1	0.137	21	Minimum spray volume 25gallons/acre for ground and 10gallons/acre for aerial.
Citrus Fruit (crop group 10-10 including Calamondin, Citrus citron, Citrus hybrids (*Citrus* spp., *Eremocitrus* spp., *Fortunella* spp., *Microcitrus* spp., and *Poncirus* spp.), Grapefruit (including Japanese summer), Kumquat, Lemon, Lime, Lime (Sweet, Australian desert, Australian finger, Australian round, Brown River finger, Mount White, New Guinea wild, Russell River, Tahiti), Mandarin (Mediterranean, Satsuma), Orange (sour, sweet, Tachibana, Trifoliate), Pummelo, Tangelo, Tangerine [includes Tangerine (mandarin or mandarin orange), Clementine, Mediterranean mandarin, Satsuma mandarin, Tangelo, Tangor, cultivars and varieties], Tangor, Uniq fruit, and cultivars, varieties and/or hybrids of these commodities).					
Foliar	0.183	-	0.365	1	Minimum retreatment interval 10 days. Minimum spray volume 2.5 gallons/acre for ground and 2 gallons/acre for aerial.[2]
Soil	0.365	1		30	Pesticide may be applied by the following methods: 1. chemigation into root-zone through low-pressure drip, trickle, micro-sprinkler or equivalent equipment; or 2. basal drench in sufficient water to move pesticide into root-zone.
Pome Fruit (crop group 11-10 including Apple, Azarole, Crabapples (Chinese apple, Chinese crab apple, Chinese flowering apple, Crab apple, Cutleaf crab apple, Florentine crab apple, Hall crab apple, Iowa crab apple, Japanese crab apple, Kai do crab apple, Manchurian crab apple, Paradise apple, Sargent's crab apple, Siberian					

Table 3.3.1. Proposed Use Pattern for Flupyradifurone					
Applic. Type	Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)	Use Directions and Limitations
crab apple, Soulard crab apple, Southern crab apple, Sweetcrab apple, Tea crab apple, Toringa crab apple, Western Crabapple, Yunnan crab apple, and varieties and/or hybrids of these), Loquat, Mayhaw, Medlar, Pear, Asian pear, Quince, Chinese quince, Japanese quince, Tejocote, and cultivars, varieties and/or hybrids of these).					
Foliar	0.183	-	0.365	14	Minimum retreatment interval 10 days. Minimum spray volume 25 gallons/acre for ground and 10 gallons/acre for aerial.
Bush Berry (crop subgroup 13-07B, except cranberry, including Aronia berry, Blueberry (*Vaccinium* spp. – highbush, lowbush and cultivars and/or hybrids of these [= all blueberry species]), Chilean guava, Currant (black, buffalo, native and red), Elderberry, European barberry, Gooseberry (*Ribes* spp.), Honeysuckle (edible), Huckleberry, Jostaberry, Juneberry, Lingonberry, Salal, Sea buckthorn, and cultivars, varieties and/or hybrids of these).					
Foliar	0.183	-	0.365	3	Minimum retreatment interval 7 days. Minimum spray volume 25 gallons/acre for ground and 2 gallons/acre for aerial.
Low Growing Berry (crop subgroup 13-07G, except cranberry, including Bearberry, Bilberry, Blueberry (lowbush), Cloudberry, Lingonberry, Muntries, Partridgeberry, Strawberry, plus cultivars, varieties and/or hybrids of these.)					
Foliar	0.183	-	0.365	0	Minimum retreatment interval 10 days. Minimum spray volume 10 gallons/acre for ground and 2 gallons/acre for aerial.
Small Fruit Vine Climbing (except Fuzzy Kiwifruit) (crop subgroup 13-07F including Amur river grape, Gooseberry (*Ribes* spp.), Grape, Kiwifruit (hardy, only), Maypop, Schisandra berry, and cultivars, varieties and/or hybrids of these					
Foliar	0.183	-	0.365	0	Minimum retreatment interval 10 days. Minimum spray volume 25 gallons/acre for ground and 10 gallons/acre for aerial.
Soil	0.365	1		30	Pesticide may be applied by the following methods: 1. chemigation into root-zone through low-pressure drip, trickle, micro-sprinkler or equivalent equipment; or 2. basal drench in sufficient water to move pesticide into root-zone.

Table 3.3.1. Proposed Use Pattern for Flupyradifurone					
Applic. Type	Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)	Use Directions and Limitations
Tree Nut (crop group 14 including Beech nut, Brazil nut, Butternut, Cashew, Chestnut, Chinquapin, Hazelnut (filbert), Hickory nut, Macadamia nut (bush nut), Pecan, Pistachio, Walnut [including black and English (Persian) walnuts]), excluding almond.					
Foliar	0.183	-	0.365	7	Minimum retreatment interval 14 days. Minimum spray volume 75 gallons/acre for ground. Do NOT apply by aerial application.
Cotton					
Foliar	0.183	-	0.365	14	Minimum retreatment interval 10 days. Minimum spray volume 10 gallons/acre for ground, 2 gallons/acre for aerial.
Prickly Pear /Cactus Pear (*opuntia spp.*), Pitaya					
Foliar	0.183	-	0.365	14	Minimum retreatment interval 7 days. Minimum spray volume 75 gallons/acre for ground. Do NOT apply by aerial application.
Coffee Beans (Import from Central America (Guatemala, Mexico) and Brazil)[3]					
Drench + Foliar	0.535 + 0.178	1 + 3	1.07	0	The minimum retreatment interval for foliar application is 15 days. Application to soil should be October to February, when the soil is the wettest.
Rotational Crops					
Crop Type	Rotational Interval (days)				
On-label	0				
With tolerance[4]	0				
Sugarcane (Florida)	14				
Rice (white and wild)	30				
All others	360				

[1] For a seeding rate of 60 lbs/acre (ExpoSAC SOP15, 03/02/2004)
[2] Minimum application volumes are for control of Asian citrus psyllid control in Florida only. For control or suppression of other pests, application volumes should be increased to provide thorough and complete coverage to obtain adequate control.
[3] Requisite translated label from Brazil was provided (MRID 48844205)
[4] Crop Group 3 has a recommended tolerance, but not a use on the proposed label.

3.4 Anticipated Exposure Pathways

Humans may be exposed to flupyradifurone in food and drinking water since flupyradifurone may be applied directly to growing crops and application may result in flupyradifurone reaching surface and ground sources of drinking water. In an occupational setting, applicators may be exposed while handling the pesticide prior to application, during seed treatment, as well as during application. There is also a potential for post-application exposure for workers re-entering treated fields.

This is the first risk assessment prepared for the proposed uses of flupyradifurone. This risk assessment considers all of the exposure pathways based on the proposed new uses of flupyradifurone.

3.5 Consideration of Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," http://www.epa.gov/environmentaljustice/resources/policy/exec_order_12898.pdf. As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the U.S. Department of Agriculture's National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age and ethnic group. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for children 1-2 years, youths, and adults entering or playing on treated areas post-application are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

4.0 Hazard Characterization and Dose-Response Assessment

Flupyradifurone is a member of the butenolide class of chemicals, which the Registrant claims to have a pesticidal mode of action similar to neonicotinoids, acting on the nicotinic acetylcholine receptor (nAchR). Analogous to neonicotinoids, flupyradifurone is thought to bind and stimulate insect nAchRs, leading to paralysis and death. The effects seen in the acute neurotoxicity study are likely related to stimulation of the nAchRs, however there is limited additional evidence in mammalian studies that the pesticidal mode of action is important to mammals.

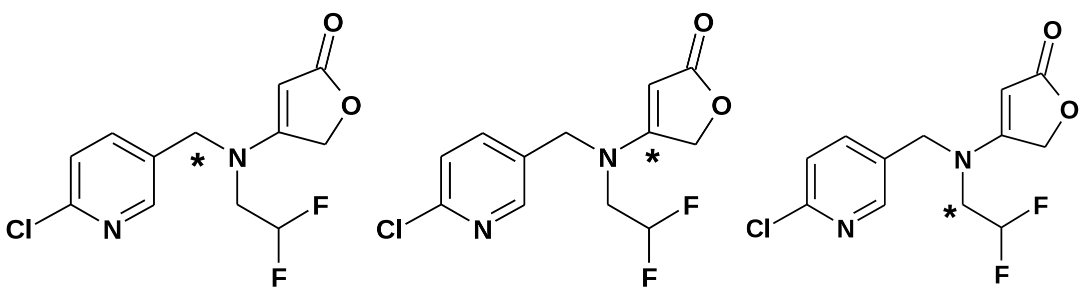
4.1 Toxicology Studies Available for Analysis

All the required toxicity studies on flupyradifurone have been submitted to support proposed food-use registrations. The toxicology database is acceptable for characterizing flupyradifurone hazard and includes 28-day oral, 90-day oral, and 28-day dermal studies in rats; 28-day oral and

90-day oral toxicity studies in mice; 28-day-oral and 90-day oral toxicity studies in dogs; a 1-year dietary study in dogs; a carcinogenicity study in mice; a 2-year dietary combined chronic/carcinogenicity in rats; developmental toxicity studies in rats and rabbits; a 2-generation reproduction study in rats; acute and subchronic neurotoxicity studies in rats; a developmental neurotoxicity study in rats; mutagenicity and genotoxicity studies in bacterial & mammalian model systems; 28-day dietary immunotoxicity studies in rats; metabolism and pharmacokinetic studies in rats with 3 different ^{14}C- labeling positions on flupyradifurone; and *in vivo* and *in vitro* dermal penetration studies on the formulated flupyradifurone. Of the available studies, some subchronic toxicity studies in rats, mice, and dogs contained data on liver enzymes, thyroid hormones, and plasma concentration of flupyradifurone. Two metabolites (DFA and difluoroethyl-amino-furanone) were tested in subchronic oral toxicity studies and in the genotoxicity battery of studies, while two other metabolites ((6-chloro-3-pyridyl) methanol and 6-chloronicotinic acid (6-CNA)) were tested only with bacterial gene mutation assays. Summaries of all toxicology studies are presented in Attachment A.

4.2 Absorption, Distribution, Metabolism, & Elimination (ADME)

Absorption, distribution, metabolism and elimination (ADME) of flupyradifurone were investigated using ^{14}C label at three different positions as shown below.



Pyridinylmethyl-^{14}C Furanone-4-^{14}C Ethyl-1-^{14}C

Regardless of labeling position, the results showed that following oral administration of a low dose (2 mg/kg) of flupyradifurone to male and female rats, the gastrointestinal absorption of radioactivity was high and accounted for >80 % of the administered dose. In most cases, the maximum plasma concentration was reached within 1 or 2 hours after dosing. With the high dose (200 mg/kg), the peak plasma concentration was observed between 2 and 4 hours after dosing. After reaching the peak concentration, the radioactivity levels in plasma declined steadily by several orders of magnitude in all studies independent of sex or labeling position of the test compound. Elimination was very fast, mainly via urine and almost completed after 24 hours. No radioactivity was detected in the expired air after dosing with the pyridinylmethyl- and ethyl-1-labeled compounds. With administration of [furanone-4-^{14}C] flupyradifurone between 1 and 3% of the administered radioactivity was detected in the expired air.

The absorbed dose was rapidly distributed; at approximately 1 hour after dosing, the concentrations in liver and kidney were significantly higher than in blood, suggesting a preferred clearance from blood and distribution mainly to the organs responsible for metabolism (liver) and excretion (kidney). Very low levels were found in the brain, spinal cord, and renal fat.

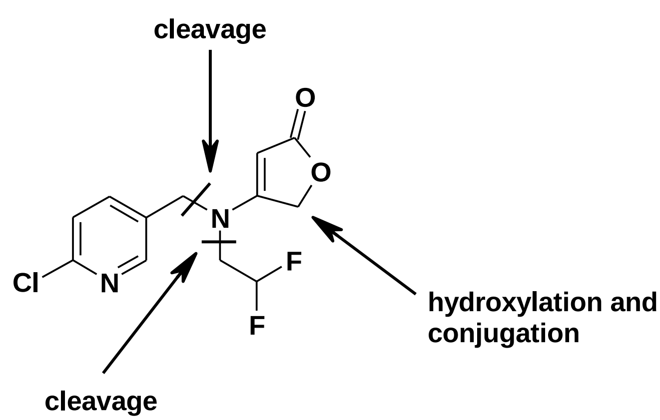
These results are similar in male and female rats independent of the labeling position. A fast decline of radioactivity concentrations was observed for all organs and tissues in males and females during the entire test period. Concentrations fell for most organs and tissues below 5% of the maximum tissue radioactivity after one day. After seven days, only very low concentrations were found in a few organs and tissues of rats. Basically, male and female rats exhibited very similar absorption, distribution, and elimination patterns. The quantitative whole body autoradiography studies demonstrated that there was no accumulation of radioactivity in any organ of the tested male and female rats.

Flupyradifurone was readily metabolized in the rat. Numerous metabolites were formed, most of them being minor. The parent compound represented the predominant part of the radioactivity in urine of male and female rats. In feces of male rats, the metabolite BYI 02960-OH was more prominent than the parent compound. Two metabolites, 6-chloro-nicotinic acid (BYI 02960-6-CNA) and BYI 02960-hippuric acid were also prominent in male but not in female rats.

The organ metabolism study using the ethyl-1-^{14}C label showed that, in the 24 hours samples of plasma, organs, and tissues, difluoroacetic acid (BYI 02960-DFA) was by far the major metabolite accounting for more than 50% of the radioactivity in the tissues. However, the BYI 02960-DFA accounted for approximately 6% of the administered dose.

The metabolic profiles in urine and feces were very similar for both sexes, but male rats showed a higher rate of metabolite formation as compared to females.

The figure below schematically shows the sites of the molecule which are involved in the metabolic reactions:



The principal metabolic reactions of flupyradifurone in rats could be summarized as follows:

- Hydroxylation followed by conjugation with glucuronic acid or sulfate;
- Cleavage of the difluoroethyl group forming BYI 02960-des-difluoroethyl, and BYI 02960-DFA;
- Cleavage of the molecule at the pyridinylmethylene bridge forming 6-chlor-nicotinic acid BYI 02960-6-CNA, which was further conjugated with glycine to BYI 02960-hippuric acid and BYI 02960-difluoroethyl-amino-furanone.

4.2.1 Dermal Absorption

There is no dermal absorption study available with technical grade flupyradifurone. However, *in vivo (rat)* and *in vitro (human and rat skin)* dermal penetration studies with the liquid (SC) formulation of flupyradifurone are available. The dermal absorption values from the 24 hour measurements from *in vivo* and *in vitro* dermal absorption studies on the most dilute test formulation (0.1 g/L of 200 g/L SL) were used to estimate the human dermal absorption factor (DAF) with the equation: *human DAF = (in vitro human % absorption) x [(in vivo rat % absorption/ (in vitro rat % absorption)]*. The calculated DAF was 7.42% for 24-hour exposure.

4.3 Toxicological Effects

The most sensitive effects seen in the flupyradifurone database were skeletal muscle atrophy/degeneration in dogs, which appear to be the most sensitive tested animal; however, with ¾ body weight scaling (Appendix A.5) the rat and dogs are equally as sensitive to the effects of flupyradifurone . With dietary administration, reductions in body weight and food consumption were commonly seen in all species of the test animals (rats, mice, dogs, and rabbits). The liver and thyroid were also common targets of flupyradifurone toxicity. The liver effects often consisted of increased liver weight, hepatocellular hypertrophy, liver enzyme increases (cytochrome p450 increases), and decreases in total cholesterol. Some of the liver effects were judged to be adaptive responses while some were correlated with vacuolations and changes in clinical chemistry parameters (increases in alkaline phosphatase (ALP) and alanine aminotranspherase (ALT), and cholesterol level changes indicative of liver effects which were progressed beyond the adaptive stage. The thyroid effects consisted of thyroid follicular cell hypertrophy and were seen mainly in rats. In addition, the thyroid effects were generally found in conjunction with liver effects.

The developmental toxicity data in rats and rabbits showed that flupyradifurone caused delayed bone ossification in the fetal rats and increase incidence of fetal death in rabbits. These effects were seen at the maternal lowest observed adverse effect levels (LOAEL, 150 mg/kg/day) in rat developmental study. No adverse maternal effects was seen at the highest tested dose (80 mg/kg/day) in the combined data of rabbit developmental studies (main and range finding studies). The increased incidence of fetal death in rabbits was considered to be both a quantitative increase in susceptibility in the developing fetuses. However, clear no observed adverse effect levels (NOAELs) were established for both rat and rabbit developmental toxicity studies.

The results of a 2-generation reproduction study showed that flupyradifurone reduced the number of estrus cycles, decreasing the number of implantations in P_2 dams, and decreasing the litter size in the presence of decreased body weight and food consumption in maternal animals. In addition, the body weight of F_2 pups was decreased at a dose (37.8 mg/kg/day) where no effect was seen in the parental animals, and this finding suggested a quantitative increase in susceptibility in the young rat.

Carcinogenicity studies in rats and mice did not yield a compound-related increase in tumor incidence, and the genotoxicity battery did not show flupyradifurone to produce any genotoxicity.

The acute neurotoxicity study showed that flupyradifurone caused increases in the incidence of piloerection and dilated pupils at 50 mg/kg. At the next higher dose level (200 mg/kg) and above, it produced a large number of clinical signs, which are indicative of neurotoxicity. These included lower muscle tone, rapid respiration, low arousal, tremors, myoclonic jerks, chewing, repetitive licking of lips, gait incoordination, flattened or hunched posture, dilated pupils, impaired (uncoordinated or slow) righting reflex, impaired flexor and tail pinch responses and reduced rectal temperature. However, none of these clinical signs were found in the dietary feeding studies, including the 90-day neurotoxicity study. The effects seen in the acute neurotoxicity study are likely related to stimulation of the nAchRs, however there is limited additional evidence in mammalian studies that the pesticidal mode of action is important to mammals. The differences in the findings between the acute neurotoxicity study and other studies using dietary administration might be explained by the rapid absorption and excretion. Flupyradifurone was absorbed rapidly in the metabolism study where rats were dosed by gavage. Peak plasma levels were reached within 1-4 hours of dosing depending on the dose, and flupyradifurone was almost completely eliminated approximately 24 hours after administration. With dietary administration, the rodent test animal consumed the compound mostly during the entire night, and the internal flupyradifurone concentration required to produce the effect was probably seldom reached due to metabolism and rapid elimination from the body. As a result, clinical signs were not reported. No neurotoxicity or other adverse effects were seen in 90-day dietary neurotoxicity study in rats at dose levels as high as 174 mg/kg/day.

No immunotoxicity was found in rats tested at the highest dose of 230 mg/kg/day.

The acute toxicity of flupyradifurone was low for all routes (oral, dermal, and inhalation). The rat oral LD_{50} was estimated to be greater than 2,000 mg/kg, with mortalities reported at 2,000 mg/kg but none at 300 mg/kg (Toxicity Category III). The acute dermal LD_{50} for rats was >2,000 mg/kg (Toxicity Category III). The acute inhalation LC_{50} for rats was >4,671 mg/m^3 (4.67 mg/L), which was the highest achievable concentration (Toxicity Category IV). Flupyradifurone was not irritating to rabbit skin and caused only slight ocular irritation (redness of the conjunctivae) which was reversed within 48 hours.

Several metabolites were found in plants and rat metabolism studies; some of these metabolites were tested in mutagenicity studies and subchronic oral toxicity studies. The results showed that most of the flupyradifurone metabolites had lower toxicity than the parent compound except difluoroacetic acid (DFA) (BCS-AA56716 see Toxicity Profile Table in Attachment A). The limited data (90-day oral feeding study in rats) showed that DFA produced a different effect from the parent compound, black foci in the glandular part of the stomach which correlated with the histopathology finding of focal glandular erosion/necrosis. In addition, slight decreases in hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, and hematocrit were also found. The stomach effects were seen at a LOAEL of 66 mg/kg/day which was lower than a comparable 90-day oral toxicity study of the parent compound in rats (LOAEL = 156 mg/kg/day). It should also be noted that when comparing the NOAEL and LOAEL of this study to a similar study (90-day oral study in dogs) with parent compound, on a molar basis, the NOAELs and LOAELs of DFA and the parent are comparable, however, the effects are different. Furthermore, it should be reiterated that in the rat metabolism study with flupyradifurone, DFA was formed and detected as approximately 6% of the administered dose.

4.4 Safety Factor for Infants and Children (FQPA Safety Factor)

Based on the currently available toxicity and exposure data, the risk assessment team recommended the FQPA Safety Factor be reduced to 1X as supported by a complete toxicological database. Although there are clinical signs which indicated neurotoxicity in adult rats and quantitative increases in susceptibility demonstrated by decreased body weights in F_2 rat pups and quantitative and qualitative susceptibility demonstrated by increased incidence of dead rabbit fetuses, there are clear NOAELs for these effects. The NOAEL for offspring toxicity in the 2-generation reproduction study is equivalent to the POD selected for risk assessment while the NOAELs for neurotoxicity (clinical signs) and rabbit development toxicity are greater than the NOAEL selected as the POD for risk assessment. Therefore, the POD is protective of the effects which are indicative of neurotoxicity and susceptibility in rats and rabbits. There is no uncertainty in the exposure database. Overall, the data support the determination that an additional safety factor is not needed. The details for reducing the FQPA safety factor are elaborated below.

4.4.1 Completeness of the Toxicology Database

The flupyradifurone toxicology database is adequate to characterize any potential for prenatal or postnatal risk for infants and children, and includes acceptable developmental toxicity studies in the rat and rabbit and a rat reproductive toxicity study, as well as acute and subchronic neurotoxicity studies. HED waived the required subchronic inhalation toxicity study based on flupyradifurone’s physical chemical properties, including low vapor pressure; low acute inhalation toxicity (Toxicity Category IV); and the use of a conservative, chronic oral POD that results in screening-level MOEs that do not exceed the target MOE for a waiver of 10X the LOC (TXR#0056903).

4.4.2 Evidence of Neurotoxicity

Although there is evidence that flupyradifurone has neurotoxic effects, EPA has a complete set of neurotoxicity studies (acute, subchronic, and developmental). The effects of those studies are well-characterized and indicate neurotoxic effects that occur at levels above the chronic POD that was selected for risk assessment. The NOAEL for the acute neurotoxicity study is being used for the acute POD. Therefore, there is no need to retain the 10X FQPA safety factor to account for any uncertainty concerning these effects.

4.4.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal

There is no evidence that flupyradifurone results in increased susceptibility in *in utero* rats or rabbits in the prenatal developmental studies or in young rats in the 2-generation reproduction study. There is quantitative susceptibility in rabbit developmental study and in the pup of the reproduction study, but the PoDs are protective of this increased susceptibility.

4.4.4 Residual Uncertainty in the Exposure Database

The exposure databases are complete or are estimated based on data that reasonably account for potential exposures. The chronic dietary exposure assessment for flupyradifurone was conservatively based on 100% crop treated (CT) assumptions, as well as conservative ground and surface drinking water modeling estimates. All of the exposure and risk estimates are based on conservative assumptions that do not underestimate risk.

4.5 Toxicity Endpoint and Point of Departure Selections

4.5.1 Dose-Response Assessment

With oral dosing, ADME of flupyradifurone was rapid. The time of peak plasma concentration was reached within 1-4 hours, depending on the dosage employed. Elimination was almost complete by 24 hours after dosing. The ADME data are consistent with the timing and doses causing effects throughout the database as there was little difference in the values of the LOAELs between the chronic study and subchronic study in either rats (90-day: 156 mg/kg/day; chronic: 120 mg/kg/day) or dogs (90-day: 33 mg/kg/day; chronic: 28 mg/kg/day). The minor differences were due to differences in dose selection. However, in the 1-year dog study, the effect seen at the LOAEL (28 mg/kg/day) was more extensive than that in the 90-day dog study. The 1-year dog study was used to establish the toxicity endpoints and POD for the chronic dietary exposure assessment. For short-term incidental oral exposure assessment and short- and intermediate-term dermal and inhalation assessment, the selection of the POD (12 mg/kg/day) and toxicity endpoint from the 90-day dog study and the 2-generation reproduction study as co-critical is appropriate and is protective of any effects seen in the developmental studies in rats and rabbits. In a similar reasoning, the 90-day dog study is also appropriate for toxicity endpoint selection for short-term dermal and inhalation exposure assessments. The duration of a 90-day dog study also corresponds to the duration of exposure for the intermediate-term dermal and inhalation exposure. The reason for employing the 2-generation reproduction study as a co-critical study in selecting the toxicity endpoint for the dermal, and inhalation exposure assessment is that the pup body weight loss occurred at similar LOAEL as the skeletal muscle atrophy/degeneration in the 90-day dog study. In addition, the pup body weight loss is a clear effect of flupyradifurone on the young animal.

The POD (35 mg/kg) selected from the acute neurotoxicity study is also protective of any effects seen in the developmental toxicity studies in rats and rabbits.

The toxicity endpoints and points of departures are presented in Table 4.5.4.1, and the rationale for the selections is presented in Appendix A.

4.5.2 Recommendation for Combining Routes of Exposures for Risk Assessment

HED combines exposure from different routes for each population if the same toxic effects are seen for that duration of exposure by each route. Since the same endpoint (skeletal muscle atrophy in the dog, co-critical with the pup body weight decrease) was chosen for both dermal and inhalation risk assessment, these exposures should be combined.

4.5.3 Cancer Classification and Risk Assessment Recommendation

Flupyradifurone is classified as "Not likely to be Carcinogenic to Humans" based on the absence of increased tumor incidence in acceptable/guideline carcinogenicity studies in rats and mice.

4.5.4 Summary of Points of Departure and Toxicity Endpoints Used in Human Risk Assessment

Table 4.5.4.1: Summary of Toxicity Endpoints and Points of Departure for Use in Dietary, Non-Occupational, and Occupational Human Health Risk Assessments.

Exposure/ Scenario	Point of Departure	Uncertainty/ FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (All populations)	NOAEL = 35 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 1x	aRfD =0.35 mg/kg/day	**Acute neurotoxicity study –rat** LOAEL = 50 mg/kg/day based on increased incidences of piloerection in both sexes and pupil dilation in females on Day 1. At the next higher dose level (200 mg/kg) or above, lower muscle tone, rapid respiration, low arousal, tremors, myoclonic jerks, chewing, repetitive licking of lips, gait incoordination, flattened or hunched posture, dilated pupils, impaired (uncoordinated or slow) righting reflex, impaired flexor and tail pinch responses and reduced rectal temperature. Automated measures of motor activity were also reduced in both sexes, compared to controls.
Chronic Dietary (All Populations)	NOAEL = 7.8 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 1x	cRfD = 0.078 mg/kg/day cPAD = 0.078 mg/kg/day	**1-year oral toxicity study-dog** LOAEL= 28 mg/kg/day based on minimal to slight, focal to multifocal areas of skeletal muscle degeneration in gastrocnemius and/or biceps femoris muscle.
Dermal Short-(1-30 days) and Intermediate-terms (1-6 months)	NOAEL = 12 mg/kg/day DAF = 7.42%[a]	UF_A= 10x UF_H=10x	LOC = 100	**90-day oral toxicity study-dog** LOAEL= 33 mg/kg/day based skeletal muscle atrophy/degeneration. **2-generation reproduction study- rat as a co-critical study.** NOAEL= 7.7 mg/kg/day Offspring LOAEL=38.7 mg/kg/day based on pup body weight decrease.
Inhalation Short-(1-30 days) and Intermediate-terms (1-6 months)	NOAEL = 12 mg/kg/day	UF_A= 10x UF_H=10x	LOC = 100	**90-day oral toxicity study-dog** LOAEL= 33 mg/kg/day based on skeletal muscle atrophy/degeneration **2-generation reproduction study- rat as a co-critical study.** NOAEL= 7.7 mg/kg/day Offspring LOAEL=38.7 mg/kg/day based on pup body weight decrease.
Cancer (oral, dermal, inhalation)	Classification: "Not likely to be Carcinogenic to Humans" based on data showing no treatment-related increase in tumors incidence in rat and mouse carcinogenicity studies. No mutagenic concern was reported in the genotoxicity studies.			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A =

extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (c = chronic). RfD = reference dose. LOC = level of concern. Dermal Absorption Factor = DAF. Toxicity via the inhalation route of exposure is assumed to be equivalent to toxicity via the oral route. [a]: This DAF was calculated based on the dermal absorption values from the 24 hours measurements of the most dilute test formulation used in the *in vivo* rat and *in vitro* human and rat skin dermal penetration studies. To estimate the human dermal absorption factor (DAF), the following equation is used:
Human DAF = *(in vitro* human % absorption*) x [(in vivo* rat % absorption*/ (in vitro* rat % absorption*)]*.

5.0 Dietary Exposure and Risk Assessment

5.1 Metabolite/Degradate Residue Profile

5.1.1 Summary of Plant and Animal Metabolism Studies

Plants
The metabolic fate of [^{14}C]-flupyradifurone was investigated in potato, apple, rice, cotton, and tomato using two radiolabeled forms of flupyradifurone (furoanone-4-^{14}C and pyridinylmethyl-^{14}C) for all crops except tomatoes, where a third radiolabel form was used (ethyl-1-^{14}C). It is noted that no metabolism study was provided for a leafy vegetable. However, the array of studies presented with similar results is adequate to translate to the remaining plant types. The metabolism of flupyradifurone was qualitatively similar in five different metabolic group types (root, fruit, cereal grain, oilseed, and fruiting vegetable) regardless of the application type (foliar, soil drench, seed). Moreover, the metabolism was similar for both longer (100 day) and shorter (20 day) PHIs. However, the relative amounts of parent and metabolites varied considerably with the crop and timing of application.

Flupyradifurone was generally a major component of the residue in all instances, although its contribution was significantly greater at the shorter PHIs typical of most proposed uses. An exception was noted in the early season only application to apple trees (PHI 98 days), where extensive metabolism/reincorporation of the radiolabel into natural products occurred (*with the [Furanone-4-^{14}C]-BYI 02960 label*) and parent was subsequently a minor component.

The soil-treatment type studies showed some total breakdown of flupyradifurone and re-incorporation of the radiolabel into carbohydrates, especially for rice and tomato. Cleavage of the parent to 6-chloro-3-pyridinemethanol (CHMP) and CHMP reaction products, hydroxylation /conjugation of the furanone moiety, cleavage of the pyridinylamine bond with formation of BYI 02960-difluoroethyl amino furanone and degradation of the furanone moiety with formation of BYI 02960 acetic acid and further metabolism products were evident. A radiolabeled study with the difluoroacetic acid moiety was conducted only for the drench application to tomato, where large amounts of radiolabeled DFA were found.

Similar paths of metabolism were observed with the foliar treatments (cotton, apple, rice). Formation of difluoroacetic acid was likely a significant pathway, as evidenced in the determination of non-radiolabeled difluoroacetic acid from the various plant extracts.

Livestock
Nature of the residue studies with separate radiolabels on the furanone and pyridinyl rings of flupyradifurone were conducted with laying hens and a lactating goat. Adequate amounts of the

administered doses were recovered in all cases. Generally, adequate amounts of the radiolabeled residues were released by solvent extraction and subsequently identified or characterized.

Metabolism in poultry was far more extensive than in ruminants. Parent flupyradifurone was generally a minor component in hen matrices, with the exception of fat (15% of the TRR) and eggs (20% of the TRR) for the pyridinyl label only. Fatty acids were the major metabolic product with the furanone label for eggs, fat, and liver, indicating extensive metabolism. With the pyridinylmethyl label, acetyl-AMCP, from cleavage of both the furanone and difluroethyl groups, was the major residue in eggs, and the major residue in liver was BYI 02960 OH-SA from hydroxylation of the furanone. Similar extensive hydroxylation to BYI 02960 OH derivatives was seen in ruminant liver.

Metabolism in ruminants was very limited. BYI 02960 was the major portion of the residue in fat, muscle, and liver. The parent was also the major component in milk with the pyridinyl label, but lactose from total breakdown and reincorporation of the radiolabeled carbon was the major component in milk for the furanone label. Significant metabolism was demonstrated only in kidney. The major metabolites were BYI 02960 OH (15%-35% of the TRR) and BYI 02960 OH-glucuonides (26%-31% of the TRR) from hydroxylation followed by conjugation with glucuronic acid.

Metabolism in livestock with [Ethyl-1-^{14}C]-BYI 02960 was not studied. Therefore, nothing can be concluded from the metabolism studies about the significance of DFA as a livestock metabolite. However, DFA was measured in the livestock feeding studies and was found is some matrices to be present in significant quantities. It was the major portion of the residue in poultry commodities.

5.1.2 Summary of Environmental Degradation

With respect to environmental fate, flupyradifurone is moderately soluble and is classified as mobile to moderately mobile. It is relatively stable to hydrolysis, soil photolysis, anaerobic soil metabolism, and anaerobic aquatic metabolism. It does degrade via aqueous photolysis with a half-life of approximately three days. Under aerobic aquatic conditions the half live values ranged from 237 to 365 days for parent alone and from 676 to 893 days for parent plus unextracted residues. The main transformation products observed were DFA and 6-CNA in aerobic and anaerobic soil metabolism studies and in field dissipation studies, while BYI 02960-succinamide and BYI 02960-azabicyclosuccinamide were present in aqueous photolysis studies. Preliminary information indicates that DFA is highly mobile and 6-CNA is mobile to moderately mobile; therefore, both have the potential to leach to groundwater.

Based on flupyradifurone's log K_{OW} value of 0.08, and log octanol-air partition coefficient (K_{OA}) values of 11, it is not likely to bioconcentrate in terrestrial organisms.[1] This is supported by the predicted short half-life in the vapor phase. Compounds with a log K_{OW} of three and above are

[1] A recent scientific advisory panel (SAP) reported, "Gobas *et al.* (2003) concluded that chemicals with a log K_{OA} > 5 can biomagnify in terrestrial food chains if log K_{OW} >2 and the rate of chemical transformation is low. However, further proof is needed before accepting these limits without reservations" (USEPA, 2009). This was also supported by Armitage and Gobas's work completed in 2007 (Armitage and Gobas, 2007).

generally considered to have the potential to bioconcentrate in aquatic organisms. Because flupyradifurone's log K_{OW} is 0.08, it is not expected to significantly bioconcentrate in aquatic organisms.

Study results indicate that flupyradifurone is persistent to very persistent[2] in soil, sediment and water.

The transformation products that are potentially important for human health drinking water exposure include the four major transformation products observed in environmental fate studies at greater than 10% applied radioactivity:

- 6-chloronicotinic acid (6-CNA),
- difluoroacetic acid (DFA),
- BYI 02960-succinamide (M48), and
- BYI 02960-azabicyclosuccinamide (M47).

6-CNA is degraded rapidly in three aerobic soil systems (the dissipation half-life, or DT_{50}, ranged from 3 to 7 days). The degradate DFA was persistent to very persistent in two aerobic aquatic systems (DT_{50} ranged from 121 to 951 days).

Dissipation half-lives for the whole soil profile ranged from 8 to 310 days. Most residues were observed in the top 15 cm at all sites; however, flupyradifurone was observed up to a depth of 40 cm. Field sites varied in percent organic carbon (ranging from 0.8 to 4.4% OM), soil properties, and pH (range from 5.5 to 8.2). Carryover of residues at the end of the sampling period ranged from 8 to 59%, indicating that flupyradifurone does have the potential to accumulate in soil over multiple applications and from year to year. Two of the major degradates observed in laboratory studies, 6-CNA and DFA, were also observed in the field studies. M47 and M48 were not looked for in the field dissipation studies.

Measured aerobic soil DT_{50}s of 38 to 401 days are uncertain because of high amounts of unextracted residues which may or may not constitute residues of concern. Half-lives calculated assuming that the unextracted residues do constitute residues of concern range from 79 to 799 days and are approximately double those for parent alone.

5.1.3 Comparison of Metabolic Pathways

The metabolic pathways in the five crops and application types (soil, foliar, seed) studied are qualitatively similar and well understood based on characterization and identification of the residues. The metabolism from the confined rotational crop study is similar to the primary crop metabolism studies. Parent BYI 02960 is generally the predominant part of the residue; where it is not predominant, a natural product (such as glucose) predominates. Difluoroacetic acid is a major metabolite, although it has been directly confirmed in only one metabolism study. The metabolites are also rat metabolites.

[2] According to the Toxic Release Inventory Classification System, chemicals with half-lives greater than 60-days are classified as persistent and chemicals with half-lives greater than 180 days are classified as very persistent (USEPA, 2012a).

On basis of the metabolites identified, transformation of flupyradifurone (BYI 02960) proceeds by the following pathways:

- oxidative cleavage of the difluoroethylamine bond and formation of difluoroacetic acid
- complete degradation of the furanone moiety and incorporation of carbon atoms into the natural compound pool, e.g. into glucose/carbohydrates
- cleavage of the pyridinylmethylamine bond and formation of BYI 02960-difluoroethylamino-furanone and its corresponding counterpart BYI 02960-CHMP, which was either conjugated with carbohydrates or oxidised to 6-chloronicotinic acid (6-CNA)
- hydroxylation of the furanone moiety or the difluoroethyl moiety followed by conjugation with carbohydrates,
- oxidative degradation of the furanone moiety to an acetic acid group followed either by conjugation with a carbohydrate or further degradation.

The metabolism in ruminants qualitatively mirrors that of plants. Metabolism is limited, with parent BYI 02960 the predominant component of the residue in all commodities. In milk, complete degradation of the parent (degradation of the furanone moiety) and reincorporation is indicated by the presence of radiolabeled lactose. Other similar metabolic pathways are indicated by the presence of 6-CNA from the cleavage of the pyridinylmethylamine bond and the presence of BYI 02960-OH-gluA from hydroxylation of the furanone moiety.

The metabolism in poultry is much more extensive than in plants or ruminants, as evidenced by the low or no concentrations of parent BYI 02960 in eggs and tissues. The majority of the radiolabeled residue was characterized as fatty acids. The minor metabolites found are consistent with metabolites found in the ruminant and in the rat. An exception is BYI 02960 acetyl-AMCP found only in poultry.

5.1.4 Residues of Concern Summary and Rationale

Primary Crops: Parent flupyradifurone, glucose, CHMP-di-glyc, 6-CNA, and DFA were identified as major residues in the primary crop metabolism studies and/or crop field trials. Glucose and CHMP-di-glyc are highly soluble and not of toxicological concern. 6-CNA has been characterized as not of toxicological concern as well, and it is expected to be rapidly metabolized and conjugated. Parent flupyradifurone and DFA are considered as residues of concern (ROC) for risk assessment due to their comparable NOAELs and LOAELs and their identification as main residues in the metabolism studies and crop field trials. However, for tolerance enforcement, parent flupyradifurone alone is considered an appropriate marker of misuse.

Rotational Crops: Parent flupyradifurone and DFA were identified as main components in the rotational crops. Other metabolites also observed in the primary crops were identified in the rotational crops, but were excluded from the ROC definition based on the absence of a toxicity concern. Parent flupyradifurone is recommended as ROC for tolerance enforcement while parent flupyradifurone and DFA are recommended as the ROCs for risk assessment.

Processed commodities: Processing studies showed that parent flupyradifurone is stable upon processing and therefore an adequate marker of misuse and tolerance enforcement in processed commodities. Parent flupyradifurone and DFA are included as the ROCs for risk assessment.

Livestock: Parent flupyradifurone and DFA are the main residues identified in the ruminant metabolism and feeding studies. Since parent flupyradifurone was observed in the feeding study, it is considered an appropriate marker of misuse on ruminant commodities and recommended as the ROC for tolerance enforcement.

The poultry feeding study showed DFA as the main residue, and parent flupyradifurone and several metabolites at low concentrations relative to DFA. Parent flupyradifurone is predicted to be at or below the LOQ of the analytical method in poultry commodities at the calculated poultry exposure level. DFA may be slightly above the LOQ in some poultry commodities at the exposure level. The ROCKS suggested that the residue definition for enforcement should include parent and DFA. However, further consultation with the international partners led to the decision to include only parent in the ROC for enforcement. DFA does not have a strong advantage as a marker for misuse, and the lack of a DFA feeding study does not allow for accurate determination of the DFA residue contribution from DFA itself. Therefore, parent flupyradifurone is the ROC for tolerance enforcement and risk assessment in poultry commodities.

Drinking Water: Parent flupyradifurone, DFA, BYI 02960-succinamide and BYI-02960-azabicyclosuccinamide are included as residues of concern for risk assessment. The aqueous photolysis degradates, BYI 02960-succinamide (M48) and BYI 02960-azabicyclosuccinamide (M47), are recommended for surface water estimates only since these are likely to be formed in clear and shallow water bodies. 6-CNA was a major transformation product in the fate studies, but is excluded as a ROC, since it is not considered of toxicity concern.

Table 5.1.4: Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression. [1, 2]

Matrix		Residues Included in Risk Assessment	Residues Included in Tolerance Expression
Plants	Primary Crop	Flupyradifurone Difluoroacetic acid	Flupyradifurone
	Rotational Crop	Flupyradifurone Difluoroacetic acid	Flupyradifurone
	Processed Commodities	Flupyradifurone Difluoroacetic acid	Flupyradifurone
Livestock	Ruminant	Flupyradifurone Difluoroacetic acid	Flupyradifurone
	Poultry	Flupyradifurone Difluoroacetic acid	Flupyradifurone
Drinking Water[2]		Flupyradifurone, Difluoroacetic acid, BYI 02960-succinamide, and BYI 02960-azabicyclosuccinamide[3]	Not Applicable[4]

[1] Difluoroacetic acid and flupyradifurone may need to be considered in separate risk assessments.
[2] Refer to Appendix 1 for the names and/or chemical structures of the metabolites/degradates.

[3] The aqueous photolysis degradates, BYI 02960-succinamide (M48) and BYI 02960-azabicyclosuccinamide (M47), are recommended for surface water estimates only.
[4] NA – Not applicable.

5.2 Food Residue Profile

There are adequate residue data on plant food and feed commodities for the purposes of risk assessment and tolerance assessment. Parent flupyradifurone is the major component of the residue in food commodities, as evidenced by the plant metabolism studies and the crop field trial studies. The parent is quantifiable with the possible exception of tree nuts, where both flupyradifurone and DFA are at or below the LOQ (0.01ppm). The crop field trials indicate that difluoroacetic acid, DFA, can be a significant portion of the residue for some commodities, most notably legume vegetables. Residues of parent generally decline with PHI, but DFA often increases with PHI and reaches a plateau around 32 – 35 days after crop treatment. This makes DFA a poor marker for tolerance enforcement purposes.

Flupyradifurone shows only a slight tendency to concentrate as a surface residue. It tends to distribute throughout the commodity, i.e., is systemic. Flupyradifurone is taken into the plant via the roots (soil drench treatment) or translaminarly through the leaf tissue (foliar treatment). The residues are qualitatively similar from both paths. Flupyradifurone is stable to the conditions of processing. It concentrates in dried (raisins) and concentrated (tomato paste) processed commodities, but does not concentrate in juices or oils. It concentrates slightly in outer surface commodities such as cereal bran. Storage stability studies on divergent commodity types demonstrated that flupyradifurone and DFA are stable in commodities stored frozen for intervals that encompass the storage of samples from the crop field trials.

Confined rotational crop studies indicated the potential for flupyradifurone residues present at very low levels at PBIs up to one year. However, flupyradifurone is proposed for use on almost all food and feed commodities, with the exception of herbs and spices, stone fruit, tropical fruit, grass animal feeds, mushrooms, rice, sugar cane, and some oilseeds. Rotational crop studies with sugarcane show that a PBI of 14 days is acceptable. Limited field rotational crop studies from Europe indicate that flupyradifurone will most likely be <0.01 ppm on rotational crop commodities at a one year PBI. For crops without a tolerance and/or a labeled use, except sugarcane, a PBI of one year is necessary.

Livestock feeding studies show that flupyradifurone does transfer to meat, milk, poultry, and eggs, but overall transfer to poultry commodities is low at the anticipated exposure levels. Adequate feeding concentration levels are available to bracket the exposure anticipated from residues of flupyradifurone on livestock feed commodities. Parent is the major component of the residue in ruminant commodities, but DFA is significant in poultry commodities. No DFA feeding studies were available for risk assessment purposes, and DFA levels in livestock commodities from the feeding of DFA (in crop matrices) were *estimated* from a mass balance analysis of the flupyradifurone feeding studies.

5.3 Water Residue Profile

Since flupyradifurone is a proposed new chemical, there are no monitoring data currently available. The estimated drinking water residues used in the dietary risk assessment were provided by EFED (K. White, D415166, 02/28/2014) and incorporated directly into the dietary exposure assessment. Estimated water residues were incorporated in the DEEM-FCID into the food categories “water, direct, all sources” and “water, indirect, all sources.” Estimated drinking water concentrations (EDWCs) were calculated for total toxic residues consisting of parent plus M47 plus M48 plus unextracted residues (referred to as “TTR-UN”). The number of growing seasons per year was not specified on the label and flupyradifurone could be used for multiple seasons per year on one site. Therefore, the estimates incorporated into the dietary assessment conservatively assumed three growing seasons per year, and resulted in the highest EDWC.

The EDWC for the acute and chronic assessment was estimated using PRZM-GW (ground water). The models used to derive the EDWCs are listed in Table 5.3.1. The models and their descriptions are available at the EPA internet site: http://www.epa.gov/oppefed1/models/water/.

Table 5.3.1. Tier I EDWCs for residues of flupyradifurone plus M47 plus M48 plus unextracted residues.[1]

Source of Drinking Water (Model)	TTR-UN concentration in drinking water (µg/L)	
	Acute	Annual Average or Post Breakthrough Average
Surface Water (Modified Tier 1 Rice Model)	112	112
Surface Water (PRZM/EXAMS)	46.1 (1 season) 47.7 (2 seasons) 52.5 (3 seasons)	13.9 (1 season) 20.1 (2 seasons) 22.3 (3 seasons)
Ground Water (PRZM-GW)	117 (1 season) 23.8 (2 seasons) **352** (3 seasons)	102 (1 season) 208 (2 seasons) **307** (3 seasons**)**

[1] For surface water, all values reflect residues of flupyradifurone plus the aqueous photolysis degradates, M47 and M48, plus unextracted residues. For groundwater, residue values reflect parent only as recommended by ROCKs because photolysis is less likely in groundwater, and because PRZM-GW models do not include inputs for photolysis. Residues in groundwater also include unextracted residues because it is uncertain whether the unextracted residues are parent or a residue of concern. Bolded values indicates values used in the acute and chronic assessments. Refinements can be made to get lower EDWCs.

5.4 Dietary Risk Assessment

5.4.1 Description of Residue Data Used in Dietary Assessment

For both acute and chronic dietary assessments, HED used recommended tolerance-level residues for the proposed crops. DEEM default processing factors were used for dried apple, dried beef, and dried pear; empirical processing factors were used for processed commodities of apple (sauce and juice), coffee, citrus oil, cotton (oil), corn (bran, flour, meal, starch, oil), grape (wine, juice), grapefruit (juice), hops (dried cones), limes (juice), lemons (juice), oranges (juice and peel), peanut (butter, oil), pears (juice), potatoes (chips, flakes, cooked), tomatoes (juice, puree, paste), soybeans (oil, milk, flour), and wheat (bran, germ, flour).

5.4.2 Percent Crop Treated Used in Dietary Assessment

The acute and chronic dietary exposure analysis assumed that 100% of the proposed crops were treated with flupyradifurone because there are currently no registered uses.

5.4.3 Acute Dietary Risk Assessment

The results of the acute analysis indicate that acute dietary (food and drinking water) exposure and risk estimates do not exceed HED's LOC [i.e., <100% acute population adjusted dose (aPAD)] for the U.S. population and all population subgroups. At the 95th percentile of exposure, the resulting acute dietary risk estimates utilized 24% of the aPAD for the general U.S. population and utilized 38% of the aPAD for children 1-2 years old, the most highly exposed population subgroup. The results of the acute dietary exposure analysis are included in Table 5.4.6.

5.4.4 Chronic Dietary Risk Assessment

The chronic dietary (food and drinking water) exposure and risk estimates do not exceed HED's LOC [i.e., <100% chronic population adjusted dose (cPAD)] for the U.S. population or any population subgroups. The resulting chronic dietary risk estimates utilized 39% of the cPAD for the general U.S. population and utilized 84% of the cPAD for children 1-2 years old, the most highly exposed population subgroup. Based on the lack of refinement in the assessment, actual dietary exposure is expected to be significantly lower.

5.4.5 Cancer Dietary Risk Assessment

Flupyradifurone is classified as "not likely to be carcinogenic to humans"; therefore a cancer dietary exposure assessment was not performed.

5.4.6 Summary Table

Table 5.4.6. Summary of Dietary (Food and Drinking Water) Exposure and Risk for Flupyradifurone.[1]

Population Subgroup	Acute Dietary (95th Percentile)		Chronic Dietary	
	Dietary Exposure (mg/kg/day)	% aPAD	Dietary Exposure (mg/kg/day)	% cPAD
General U.S. Population	0.082755	24	0.030629	39
All Infants (<1 year old)	0.100233	29	0.038123	49
Children 1-2 years old*	**0.133852**	**38**	**0.065155**	**84**
Children 3-5 years old	0.131183	37	0.055003	71
Children 6-12 years old	0.083856	24	0.035222	45
Youth 13-19 years old	0.063792	18	0.024110	31
Adults 20-49 years old	0.076762	22	0.028118	36
Adults 50-99 years old	0.075170	21	0.027976	36
Females 13-49 years old	0.080078	23	0.028251	36

[1]The subpopulation with the highest risk estimate is bolded.

5.5 Dietary Exposure Evaluation - DFA

Studies submitted in support of the registration of flupyradifurone indicated that there could be exposure to DFA in food (plant and animal based) and drinking water. DFA was also shown to be a mammalian metabolite; approximately 6% of flupyradifurone administered to rats was converted to DFA, and DFA was a metabolite in the ruminant and poultry metabolism studies. The most sensitive toxic effects to be used in the risk assessment for flupyradifurone would not be expected from DFA, which has a very different chemical structure. A range-finding and subchronic toxicity study with DFA showed different toxic effects (black foci in the glandular part of the stomach) than the parent compound (skeletal muscle atrophy and degeneration), indicating that risk from DFA should be assessed separately from the parent. DFA is much more polar than the parent compound as well; which indicates it may be excreted rapidly. HED conducted a screening-level evaluation of DFA to determine if there were any residual concerns for exposure to DFA. This evaluation assumed conservative drinking water concentrations, that 100% of the crops contained DFA at median residue values for all crops except when individual median residues were available. For livestock, dietary burdens were calculated based on DFA tissue to flupyradifurone feed ratios. Using these conservative inputs, exposure to DFA is 7X less than estimated exposure to flupyradifurone for the general US population, and 5X less than estimated exposure to flupyradifurone for children 1-2 years old, the highest exposed population subgroup. Therefore, since there is similar potency (albeit with different toxic effects) between flupyradifurone and DFA, but less exposure expected to DFA than the flupyradifurone, the Agency has no additional risk concerns about exposure to DFA.

6.0 Residential (Non-Occupational) Exposure/Risk Characterization

There are no proposed residential uses of flupyradifurone; therefore, a residential exposure assessment has not been conducted. A turf transferrable residue (TTR) study is not required for flupyradifurone at this time because there are no proposed uses on turf.

6.1 Residential Bystander Post-application Inhalation Exposure

Based on the Agency's current practices, a quantitative post-application inhalation exposure assessment was not performed for flupyradifurone at this time primarily because of the low acute inhalation toxicity (Toxicity Category IV), low vapor pressure (7.0×10^{-9} mm Hg at 20^{o}C), and the low proposed use rate (0.365 lb ai/A). However, volatilization of pesticides may be a source of post-application inhalation exposure to individuals nearby pesticide applications. The Agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010[3]. The Agency is in the process of evaluating the SAP report and may, as appropriate, develop policies and procedures to identify the need for and, subsequently, the way to incorporate post-application inhalation exposure into the Agency's risk assessments. If new policies or procedures are developed, the Agency may revisit the need for a quantitative post-application inhalation exposure assessment for flupyradifurone.

[3] Available: http://www.epa.gov/scipoly/SAP/meetings/2009/120109meeting.html

6.2 Spray Drift

Spray drift is a potential source of exposure to those nearby pesticide applications. This is particularly the case with aerial application, but, to a lesser extent, spray drift can also be a potential source of exposure from the ground application methods (e.g., groundboom and airblast) employed for flupyradifurone. The Agency has been working with the Spray Drift Task Force (a task force composed of various registrants which was developed as a result of a Data Call-In issued by EPA), EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices (see the Agency's Spray Drift website for more information).[4] The Agency is also taking means to qualitatively and qualitatively address spray drift as a potential source of exposure in risk assessments for pesticides through existing programs such as Ag Drift and chemical specific properties of pesticides. The potential for spray drift will be quantitatively evaluated for each pesticide during the *Registration Review* process which ensures that all uses for that pesticide will be considered concurrently.

7.0 Aggregate Exposure/Risk Characterization

In accordance with the FQPA, HED must consider and aggregate (add) pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure. There are no residential uses of flupyradifurone; therefore, the aggregate risk includes only exposure from food and drinking water. Acute and chronic dietary risks do not exceed HED's LOC for the U.S. population or any population subgroups. Refer to Section 5.0 for the dietary exposure estimates.

8.0 Cumulative Exposure/Risk Characterization

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to flupyradifurone and any other substances and flupyradifurone does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that flupyradifurone has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

[4] Available: http://www.epa.gov/opp00001/factsheets/spraydrift.htm

9.0 Occupational Exposure/Risk Characterization

9.1 Short-/Intermediate-Term Occupational Handler Risk

There is potential for short- and intermediate-term occupational exposure to flupyradifurone during both handler [mixing, loading, and application (via the dermal and inhalation routes)] and post-application activities (via the dermal route) based on the proposed uses.

Additionally, for both dermal and inhalation exposures, the PODs selected are considered protective of both short- and intermediate-term durations.

The quantitative exposure/risk assessment developed for occupational handlers is based on the following scenarios:

- Mixing/Loading liquid formulations for aerial, airblast, chemigation, and groundboom application;
- Applying sprays with aerial, airblast, and groundboom equipment;
- Flagging for aerial applications;
- Mixing/Loading/Applying using a backpack sprayer and mechanically pressurized handgun;
- Primary handling for seed treatment (loading/applying, sewing, bagging treated seed; multiple activities); and
- Secondary handling for seed treatment (planters).

Results are presented for “baseline,” defined as a single layer of clothing consisting of a long sleeved shirt, long pants, shoes plus socks, no protective gloves, and no respirator, as well as baseline with various levels of PPE as necessary (e.g., gloves, respirator, etc). The proposed BYI 02960 480 FS (EPA Reg. No. 264-RRUE) label requires seed treaters and workers cleaning the treatment facilities to wear long sleeved shirts, long pants, shoes, socks, and chemical resistant gloves. Baggers and others involved in the packaging of treated seed are required to wear long sleeved shirts, long pants, shoes, and socks. The proposed Sivanto™ (EPA Reg. No. 264-RRUR) label requires occupational handlers to wear long sleeved shirts, long pants, shoes, socks, and chemical resistant gloves.

There are no risk estimates of concern at baseline (no PPE). For the agricultural uses of flupyradifurone, the short- and intermediate-term combined (dermal + inhalation) occupational handler MOEs ranged from 260 to 17,000 with baseline PPE. With the addition of chemical resistant gloves, as required on the flupyradifurone label, the short- and intermediate-term combined (dermal + inhalation) occupational handler MOEs ranged from 800 to 57,000. For the proposed seed treatment use of flupyradifurone, the combined (dermal + inhalation) short- and intermediate-term MOEs ranged from 2,000 to 14,000. The occupational handler MOE estimates are presented in Appendix F.

9.2 Short-/Intermediate-Term Post-Application Risk

9.2.1 Dermal Post-application Risk

HED uses the term post-application to describe exposures that occur when individuals are present in an environment that has been previously treated with a pesticide (also referred to as re-entry exposure). Such exposures may occur when workers enter previously treated areas to perform job functions, including activities related to crop production, such as scouting for pests or harvesting. For flupyradifurone, both short- and intermediate-term post-application exposure could occur for the proposed agricultural uses. It may be applied throughout the growth season, including pre-bloom, during bloom, or following bloom, increasing the likelihood of exposure during post-application activities. However, because the POD is the same for dermal short- and intermediate-term exposures, one assessment is protective of both durations.

Chemical-specific dislodgeable foliar residue data have not been submitted for flupyradifurone. Therefore, this assessment uses HED's default assumption that 25% of the application is available for transfer on day 0 following the application and the residues dissipate at a rate of 10% each following day.

The occupational short- and intermediate-term dermal post-application risk estimates ranged from 170 to 15,000 on the day of application. A summary of the anticipated worst-case post-application activities and associated transfer coefficients and MOEs for the proposed crops/use sites is provided in Appendix F.

In accordance with 40CFR158, DFR data are required for all occupational (e.g., crop, nursery, greenhouse use sites) or residential (e.g., ornamental and vegetable gardens, pick your own farms, retail tree farms) uses that could result in post-application exposure to foliage. In the absence of chemical-specific DFR data, EPA uses default values. The *2012 Standard Operating Procedures for Residential Pesticide Exposure Assessment* includes an analysis of a number of DFR studies, which resulted in the selection of a revised default values for the fraction of the application rate available for transfer after a foliar application (F_{AR}). These values are based on an analysis of 19 DFR studies. Since that time, the Agricultural Re-entry Task Force has submitted information (MRID 49299201) that corrects an application rate error made in the original submission of "ARF039 – Determination of Dermal and Inhalation Exposure to Reentry Workers During Chrysanthemum Pinching in a Greenhouse" (EPA MRID 45344501). As a result, the range of F_{AR} values was revised from 2% - 89% to 2% - 47%. In the data, a large range of transferability is observed and this variability can potentially be attributable to many factors such as active ingredient; formulation; field conditions in the studies; weather conditions (e.g., humidity); or many other difficult to quantify factors. Although witnessed across multiple chemicals, this range in F_{AR} values is not expected when considering DFR data for a single chemical. At this time, the ARTF submission did not alter the selection of 25% as the reasonable, high-end default value. Because DFR data are not available for flupyradifurone, EPA is using the default value of 25%. Although there may be a small degree of uncertainty in the use of the default DFR value for flupyradifurone (i.e., there is a small chance that the F_{AR} value may exceed the applicable default value), it is likely that the health-protective aspects of EPA's occupational post-application assessment methodology will more than compensate for this potential uncertainty. For example, when assessing residential and occupational post-application exposure to gardens and ornamentals, EPA assumes the following: exposures occur to zero-day (i.e., day of application) residues every day of the assessed exposure duration (i.e., EPA assumes that no dissipation or degradation occurs, it doesn't rain, etc); individuals perform the same post-application activities performed in the transfer coefficient study day after day (e.g., weeding, harvesting, pruning, etc.); and individuals engage in these post-application activities for a high-end amount of time every day (represented by data reflecting time spent gardening based on survey data).

Given the conservatisms discussed above and the potential compounding nature of these conservatisms, EPA is able to rely upon the calculated exposure estimates with confidence that exposure is not being underestimated.

However, since the highest estimated occupational post-application exposure using default DFR values for flupyradifurone is not minimal in comparison to the level of concern (i.e., the calculated MOE is not greater than 2 times higher than the level of concern, MOE = 170 compared to the LOC of 100); EPA is requiring the 40CFR DFR data. **Therefore, EPA is requiring the 40CFR DFR data requirement to facilitate any necessary exposure assessments refinements and to further EPA's general understanding of the availability of dislodgeable foliar pesticide residues. The studies should be conducted on three dissimilar crops; however, HED specifically recommends including grapes in the studies.**

9.2.2 Inhalation Post-application Risk

Based on the Agency's current practices, a quantitative post-application inhalation exposure assessment was not performed for flupyradifurone at this time primarily because of the low acute inhalation toxicity (Toxicity Category IV), low vapor pressure (7.0 x 10^{-9} mm Hg at 20^{o}C), and the low proposed use rate (0.365 lb ai/A). However, there are multiple potential sources of post-application inhalation exposure to individuals performing post-application activities in previously treated fields. These potential sources include volatilization of pesticides and resuspension of dusts and/or particulates that contain pesticides. The Agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010[5]. The Agency is in the process of evaluating the SAP report as well as available post-application inhalation exposure data generated by the ARTF and may, as appropriate, develop policies and procedures, to identify the need for and, subsequently, the way to incorporate occupational post-application inhalation exposure into the Agency's risk assessments. If new policies or procedures are put into place, the Agency may revisit the need for a quantitative occupational post-application inhalation exposure assessment for flupyradifurone.

Although a quantitative occupational post-application inhalation exposure assessment was not performed, an inhalation exposure assessment was performed for occupational/commercial handlers. Handler exposure resulting from application of pesticides outdoors is likely to result in higher exposure than post-application exposure. Therefore, it is expected that these handler

[5] Available: http://www.epa.gov/scipoly/SAP/meetings/2009/120109meeting.html

inhalation exposure estimates would be protective of most occupational post-application inhalation exposure scenarios.

Furthermore, inhalation exposure during dusty mechanical activities such as shaking and mechanical harvesting of tree crops is another potential source of post-application inhalation exposure. However, the airblast applicator scenario is believed to represent a reasonable worst case surrogate estimate of post-application inhalation exposure during these dusty mechanical harvesting activities. The non-cancer inhalation risk estimate for commercial airblast application does not exceed the Agency's LOC (i.e., MOE < 100).

A post-application inhalation exposure assessment is not required as exposure is expected to be negligible. Seed treatment assessments provide quantitative inhalation exposure assessments for seed treaters and secondary handlers (i.e., planters). It is expected that these exposure estimates would be protective of most post-application inhalation exposure scenarios.

10.0 References

Ideliz Negrón-Encarnación, D413192, 12/19/2013. **Flupyradifurone**. Report of the Residues of Concern Knowledgebase Subcommittee (ROCKS).

Jessica Kidwell, 03/18/2014. **Flupyradifurone** - Summary of Toxicology Science Advisory Council (ToxSAC) Meeting of February 6, 2014.

K. Rury, D413190, 04/08/2014. **Flupyradifurone:** Acute and Chronic Aggregate Dietary (Food and Drinking Water) Exposure and Risk Assessments for Proposed New Uses of the New Active Ingredient, Flupyradifurone on Soybean Seeds and the Following Agricultural Crops: *Brassica;* Bushberries, except Cranberry; Cereal Grains; Citrus; Cotton; Cucurbits; Fruiting Vegetables; Hops; Leafy Vegetables; Legumes; Low Growing Berries; Non-Grass Animal Feeds; Peanuts; Pome Fruit; Prickly Pears; Root Vegetables; Small Vine Climbing Fruit; Tree Nuts, except Almonds; and Tuberous and Corm Vegetables.

K. Rury, D413494, 04/08/2014. **Flupyradifurone.** Occupational and Residential Exposure Assessment for a New Insecticide Active Ingredient Proposed for Use on Soybean Seeds and the Following Agricultural Crops: *Brassica;* Bushberries, except Cranberry; Cereal Grains; Citrus; Cotton; Cucurbits; Fruiting Vegetables; Hops; Leafy Vegetables; Legumes; Low Growing Berries; Non-Grass Animal Feeds; Peanuts; Pome Fruit; Prickly Pears; Root Vegetables; Small Vine Climbing Fruit; Tree Nuts, except Almonds; and Tuberous and Corm Vegetables.

K. White, D415166, 02/18/2014. Drinking Water Exposure Assessment for the Section 3 New Chemical Registration for use of Flupyradifurone on a Variety of Agricultural Crops.

H. Lantum; R. Baggs, D Krenitsky; M Anders, 12/2002. Nephrotoxicity of Chlorofluoroacetic Acid in Rats. Toxicological Science 70(2): 261-8.

Monique Perron, TXR#0056903, 03/08/2014. **Flypyradifurone:** Summary of the Hazard and Science Policy Council (HASPOC) Meeting of February 20th: Waiver for a Subchronic Inhalation Study.

S. Funk, D415670, D413191, D415685, 02/17/2014. **Flupyradifurone**. First Food Use. Petition for the Establishment of Permanent Tolerances and Registration for Use on Root Vegetables Except Sugar Beet (Subgroup 1B), Tuberous and Corm Vegetables (Subgroup 1C), Bulb Vegetables (Group 3-07), Leafy Vegetables (Except *Brassica*) (Group 4), Taro Leaves, Turnip Tops; Head and Stem *Brassica* Vegetables (Subgroup 5A), Leafy *Brassica* Greens Vegetables (Subgroup 5B), Edible-Podded Legume Vegetables (Subgroup 6A), Succulent Shelled Pea and Bean (Subgroup 6B), Died Shelled Pea and Bean (except Soybean) (Subgroup 6C), Foliage of Legume Vegetables (except Soybean) (Subgroup 7A), Soybean (Seed), Fruiting Vegetables Except Cucurbits (Group 8-10), Cucurbit Vegetables (Group 9), Citrus Fruits (Group 10-10), Pome Fruits (Group 11-10), Bushberry (Subgroup 13-07B), Small Fruit Vine Climbing (Except Fuzzy Kiwifruit) (Subgroup 13-07F), Low Growing Berry (Subgroup 13-07G), Tree Nuts (Group 14-12), Cereal Grains Except Rice (Crop Group 15, Except Rice), Forage, Fodder and Straw of Cereal Grains (Crop Group 16), Nongrass Animal Feeds (Forage, Fodder, Straw and Hay) (Group 18), Cottonseed (Subgroup 20C), Coffee, Hops, Peanuts, Prickly Pear Cactus, and Pitaya. Summary of Analytical Chemistry and Residue Data.

Appendix A. Toxicology Profile and Executive Summaries

A.1 Toxicology Data Requirements

The requirements (40 CFR 158.340) for the proposed food uses of flupyradifurone are in Table A. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Table A.1: Toxicology Data Requirements of Flupyradifurone.		
Study	**Technical**	
	Required	**Satisfied**
870.1100 Acute Oral Toxicity	yes	yes
870.1200 Acute Dermal Toxicity	yes	yes
870.1300 Acute Inhalation Toxicity	yes	yes
870.2400 Primary Eye Irritation	yes	yes
870.2500 Primary Dermal Irritation	yes	yes
870.2600 Dermal Sensitization	yes	yes
870.3100 Oral Subchronic (rodent)	yes	yes
870.3150 Oral Subchronic (nonrodent)	yes	yes
870.3200 21-Day Dermal	yes	yes
870.3250 90-Day Dermal	no	no
870.3465 90-Day Inhalation	CR	yes*
870.3700a Developmental Toxicity (rodent)	yes	yes
870.3700b Developmental Toxicity (nonrodent)	yes	yes
870.3800 Reproduction	yes	yes
870.4100a Chronic Toxicity (rodent)	yes	yes
870.4100b Chronic Toxicity (nonrodent)	yes	yes
870.4200a Oncogenicity (rat)	yes	yes
870.4200b Oncogenicity (mouse)	yes	yes
870.4300 Chronic/Oncogenicity	yes	yes
870.5100 Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300 Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5375 Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5550 Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a Acute Delayed Neurotoxicity (hen)	no	-
870.6100b 90-Day Neurotoxicity (hen)	no	-
870.6200a Acute Neurotoxicity Screening Battery (rat)	yes	yes
870.6200b 90-Day Neurotoxicity Screening Battery (rat)	yes	yes
870.6300 Develop. Neurotoxicity	CR	yes
870.7485 General Metabolism	yes	yes
870.7600 Dermal Penetration	yes	yes
870.7800 Immunotoxicity	yes	yes
Special Studies for Ocular Effects		
Acute Oral (rat)	no	-
Subchronic Oral (rat)	no	-
Six-month Oral (dog)	no	-

*Study waived by HASPOC (TXR# 0056903).

A.2 Toxicity Profiles

Table A.2.1. Acute Toxicity Profile – Flupyradifurone.				
OPPTS Guideline No.	**Study Type**	**MRID**	**Results**	**Toxicity Category**
870.1000	Acute Oral - rat	48844101	LD_{50} cut off $\geq$ 2000 mg/kg (HDT) 1/3 death In ACN 2/12 test animals died at 800 mg/kg	III
870.1200	Acute Dermal- Rabbit	48844104	LD_{50} > 2000 mg/kg	III
870.1300	Acute Inhalation - Rat	48844105	LC_{50} > 4671 mg/m^3 (4.67 mg/L)	IV
870.2400	Primary Eye Irritation - Rabbit	48844106	Redness of the conjunctivae, reversed within 48 hours (score 2)	IV
870.2500	Primary Dermal Irritation - Rabbit	48844107	Non-irritating	IV
870.2600	Dermal Sensitization - mouse	48844108	Non-sensitizing	NA

Table A.2.2. Repeated dosing, neurotoxicity, mutagenicity, and metabolism studies on Flupyradifurone.			
Guideline No.	**Study Type**	**MRID No. (Date)/Classification/ Doses**	**Results**
Subchronic toxicity studies			
870.3100 (28-day)	28-day oral toxicity study in rats (gavage)	48844149 (2012) Acceptable /non-guideline 0, 75, 200, 350 mg/kg/day	NOAEL= 75 mg/kg/day LOAEL = 200 mg/kg/day based on decreased food consumption in females; increases in ALT, creatinine, & triglycerides in females, enlarged and prominent lobulation of the liver in males, diffused follicular cell hypertrophy of the thyroid in male. Cytochrome P-450 was induced.
	28-day oral toxicity study in rats (diet)	48844150 (2012) Acceptable/non-guideline 0, 500, 5000 ppm 0, 33.6, 385 mg/kg/day	NOAEL= 33.6 mg/kg/day LOAEL = 385 mg/kg/day based on decreases in body weight, and food consumption; decreases in glucose and total bilirubin; and increases in urea nitrogen and total cholesterol; prominent lobulation of the liver, and diffused follicular cell hypertrophy of the liver.
	28-day oral toxicity in mice (diet0	48844151 (2007) Acceptable/non-guideline 0, 300, 600, 1200 ppm M: 0, 40, 78, 166 mg/kg/day F: 0, 47, 98, 192 mg/kg/day	NOAEL = 166/199 mg/kg/day (M/F) (HDT)
	28-day oral toxicity in dogs (diet) (2 dogs/sex/dose)	48844152 (2008) Acceptable/non-guideline 0, 500, 2000, 4000 ppm M: 16, 62, 118 mg/kg/day F: 0, 19, 77, 131 mg/kg/day	NOAEL = 62 mg/kg/day LOAEL = 118 mg/kg/day based on increased thyroid weights, enlarged thyroid, diffuse follicular dilatation of the thyroid, and decreased food consumption.
870.3100 (90-day)	90-day oral toxicity –rats (diet)	48844111 (2012) Acceptable/Guideline 0, 100, 500, 2500 ppm M: 0, 6.0, 30.2, 156 mg/kg/day F:0, 7.6, 38.3, 186 mg/kg/day	NOAEL = 38 mg/kg/day LOAEL = 156 mg/kg/day based on dark colored thyroid associated with follicular cell hypertrophy. Body weight was slightly decreased.

Table A.2.2. **Repeated dosing, neurotoxicity, mutagenicity, and metabolism studies on Flupyradifurone.**			
Guideline No.	**Study Type**	**MRID No. (Date)/Classification/ Doses**	**Results**
	90-day oral toxicity –mouse (diet)	48844112 (2012) Acceptable/Guideline 0, 100, 500, 2500 ppm M:0, 15.6, 80.7 407 mg/kg/day F: 0, 18.8, 98.2, 473 mg/kg/day	NOAEL = 81 mg/kg/day LOAEL = 407 mg/kg/day based on consistent decreases in body weight (>10%), liver effects (↑ ALP and ALT, ↓ in total cholesterol, ↑ in absolute and relative liver weights, ↑ in incidence of moderate diffuse hepatocellular hypertrophy). Kidney effects (changes in clinical chemistry parameters and loss of multifocal/diffuse cortical epithelial cell vacuolation & increases in urea).
870.3150	90-oral toxicity-dogs (diet)	48844114 (2012) 0, 400, 1200, 3600/2400 ppm (on week 9 reduced from 3600 to 2400 ppm due to toxicity of the legs) M: 0, 12, 33, 102/85 mg/kg/day F: 0, 12, 41, 107/78 mg/kg/day	NOAEL = 12 mg/kg/day LOAEL= 33 mg/kg/day based on skeletal muscle myofiber atrophy/degeneration decreases in body weight towards the end of the study (7-9%).
870.3200	28-day dermal toxicity study in rabbits.	48844115 (2012) Acceptable/guideline 0, 50, 150, 500 mg/kg/day	NOAEL= 500 mg/kg/day (HDT). No adverse effect was seen at any test groups.
870.3456	Subchronic inhalation-toxicity study in rats.	Not available.	HASPOC reviewed the data waiver request from the Registrant. A subchronic inhalation study is not required for flupyradifurone at this time (TXR 0056903).
Chronic toxicity studies			
870.4100	Chronic oral toxicity study in dogs. (1-year; diet)	48844121 (2012) Acceptable/Guideline 0, 150, 300, 1000 ppm M: 0, 4.6, 7.8, 28.1 mg/kg/day F: 0, 4.1, 7.8, 28.2 mg/kg/day	NOAEL= 7.8 mg/kg/day LOAEL= 28 mg/kg/day based on minimal to slight, focal to multifocal areas of skeletal muscle degeneration in gastrocnemius and/or biceps femoris muscle.
870.4300	Combined chronic/ carcinogenicity study in rats.	48844123 (2012) Acceptable/guideline 0, 80, 400, 2000 ppm M: 0, 3.2, 15.8, 80.9 mg/kg/day F: 0, 4.5, 22.5, 120 mg/kg/day Interim sac. at 52 weeks (10/sex/dose)	NOAEL = 15.8 / 22.5 mg/kg/day (M/F) LOAEL = 81/ 120 mg/kg/day (M/F) based on decreases on body weight and body weight gains in females, lens opacity in females, liver effects (macrovacuolation, increased liver weight, eosinophilic/tigroid/mixed foci of hepatocellular alterations increased brown pigmentation), thyroid colloidal alteration and follicular hypertrophy, and lung effects (fomay macrophages and chronic interstitial and perivascular inflammation). In addition, iridial Mydriasis and retinal fundus were also seen.
870.4200	Carcinogenicity study in mice.	48844122 (2012) Acceptable/guideline 0, 70, 300, 1500 ppm M: 0, 10, 43, 224 mg/kg/day F: 0, 12, 53, 263 mg/kg/day Interim sac. at 52 weeks (10/sec/dose)	NOAEL = 43 mg/kg/day LOAEL = 224 mg/kg/day based on a combination decreases in terminal body weights (slight) and body weight gains. Liver weight increases with associated finding of diffuse hepatocellular vacuolation.
Developmental and reproductive toxicity studies			

Table A.2.2. **Repeated dosing, neurotoxicity, mutagenicity, and metabolism studies on Flupyradifurone.**			
Guideline No.	**Study Type**	**MRID No. (Date)/Classification/ Doses**	**Results**
870.3700	Developmental toxicity - rabbit. (gavage)	48844117 (2012) (main study) Acceptable/non-guideline 0, 7.5, 15, 40 mg/kg/day 49113601 (2013) Range finding study 0, 15, 40, & 80 mg/kg/day	Combined data from both the main and the range finding study. Maternal NOAEL = 80 mg/kg/day Maternal LOAEL could not be established. Developmental NOAEL = 40 mg/kg/day Developmental LOAEL = 80 mg/kg/day based increases in the number of dead fetuses and dead fetus per litter. Reduced fetal body weight (8%).
870.3700	Developmental toxicity –rat (gavage)	48844116 (2012) Acceptable/guideline 0, 15, 50, 150 mg/kg/day	Maternal NOAEL = 50 mg/kg/day Maternal LOAEL = 150 mg/kg/day based increased incidence of salivation and decreased food consumption. Developmental NOAEL = 50 mg/kg/day Developmental LOAEL =150 mg/kg/day based on increased incidence of incomplete parietal and hyoid centrum skull bone ossification.
870.3800	2-Generation reproduction study in rats.	48844119 (2011) Acceptable/Guideline 0, 100, 500, 1800 ppm Premating P_1 M: 0, 6.6, 32.5, 117 mg/kg/day F: 7.7, 38.7, 137 mg/kg/day	Parental NOAEL = 38.7 mg/kg/day Parental LOAEL = 137 mg/kg/day based on decreased body weights Reproductive NOAEL = 38.7 mg/kg/day Reproductive LOAEL = 137 mg/kg/day based on reduced number of estrus cycles Offspring NOAEL = 7.7 mg/kg/day Offspring LOAEL = 38.7 mg/kg/day based on decreases in pup body weights and pup body weight gains in F_2 pups.
Neurotoxicity studies			
870.6200a	Acute neurotoxicity in rats. (gavage)	48844138 (2011) Acceptable / Guideline 0, 20, 35, 50, 200, 800 mg/kg	NOAEL = 35 mg/kg/day LOAEL = 50 mg/kg/day based on increased incidences of pupil dilation in females on Day 1and piloerection in both sexes. At the next higher dose level (200 mg/kg) or above, the observed effects included lower muscle tone, rapid respiration, low arousal, tremors, myoclonic jerks, chewing, repetitive licking of lips, gait incoordination, flattened or hunched posture, dilated pupils, impaired (uncoordinated or slow) righting reflex, impaired flexor and tail pinch responses and reduced rectal temperature. Automated measures of motor activity were also reduced in both sexes, compared to controls.
870.6200b	Subchronic neurotoxicity study in rats.	48844139 (2011) Acceptable / Guideline 0, 100, 500, 2500 ppm M: 0, 5.7, 29.4, 143 mg/kg/day F: 0, 6.9, 34.8, 173 mg/kg/day	NOAEL = 34.8 mg/kg/day LOAEL = 143 mg/kg/day based on decreased body weight in both sexes Neurotoxicity was not observed at the doses tested.
870.6300	Developmental neurotoxicity study in rats.	434203011 (2012) Acceptable/guideline 0, 120, 500, 1200 ppm 0, 10.3, 42.4, 102 mg/kg/day	Maternal NOAEL = 102 mg/kg/day (HDT) Offspring NOAEL = 42 mg/kg/day Offspring LOAEL = 102 mg/kg/day based on statistically significant increases in startle response amplitude.

Table A.2.2. **Repeated dosing, neurotoxicity, mutagenicity, and metabolism studies on Flupyradifurone.**

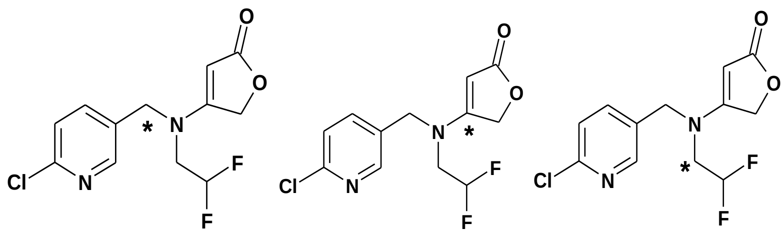
Guideline No.	Study Type	MRID No. (Date)/Classification/ Doses	Results
Metabolism studies: It should be noted that absorption, distribution, metabolism, and elimination (ADME) of flupyradifurone was conducted using three different labeling positions: ^{14}C in the pyridinlylmethylene bridge, in the 4-position of furanone ring and in the 1 position of the ethyl side chain as indicated below:  Pyridinylmethyl-^{14}C Furanone-4-^{14}C Ethyl-1-^{14}C			
870.7485	ADME with [pyridinylmethyl-^{14}C] BYI 02960-male Wistar rats	48844141 (2012) Acceptable/guideline Single gavage dose at 2 or 200 mg/kg	The absorption started immediately after dosing with the peak plasma concentration (C_{max}) reached approximately 1 hour after administration in the low dose tests and within approximately 2 to 4 hours in the high dose tests. The distribution of the radioactivity within the body was fast. From the maximum plasma level (C_{max}), the radioactivity level declined slowly down to approximately 50% of C_{max} after 4 – 8 hours in the low dose tests and after 8 – 24 hours in the high dose tests and down to low values around the LOQ in the low dose tests and to approximately 0.5% of C_{max} in the high dose tests by study termination (72 hours). Elimination was rapid, mainly by the renal route and essentially complete by 72 hours post dosing. Female rats exhibited slightly higher renal excretion rates of approximately 86% and 90% of the administered dose compared to approximately 76% of the dose in males. Faecal elimination accounted for approximately 23–26% of the total administered dose in males, and 7–10% in females. At the time of sacrifice, 72 hours after administration, the radioactive residues in organs and tissues were low, and only trace amounts of approx. <0.1 – 0.3% of the total administered dose was detected in the body and in the GIT. The principal metabolic reactions of [pyridinylmethyl-14C]BYI 02960 in rats were: (1) hydroxylation followed by conjugation with glucuronic acid to or with sulphate; (2) cleavage of the difluoroethyl group forming BYI 02960-des-difluoroethyl; and cleavage of the molecule at the pyridinylmethyl bridge forming BYI 02960-6-CNA, which was further conjugated with glycine to BYI 02960-hippuric acid. Parent compound, three major (BYI 02960-OH, BYI 02960-6-CNA and BYI 02960-hippuric acid) and five minor metabolites were isolated from urine and four of them identified by spectroscopic methods.
	[Pyridinylmethyl-^{14}C] whole body autoradiography-rat	48844142 (2011a) Acceptable/guideline A single gavage dose of 5 mg/kg [pyridinylmethyl-^{14}C]BYI02960 in 0.5% aqueous Tragacanth®.	The data demonstrate that BYI 02960 was readily absorbed from the gastrointestinal tract and distributed throughout the body immediately after administration. In male and female rats, maximum residue levels were reached for nearly all organs and tissues at one hour after administration. At this time, the levels for liver and kidney

Table A.2.2. Repeated dosing, neurotoxicity, mutagenicity, and metabolism studies on Flupyradifurone.			
Guideline No.	**Study Type**	**MRID No. (Date)/Classification/ Doses**	**Results**
			were significantly higher than in blood, suggesting a preferred clearance from blood and distribution mainly to those organs that are responsible for metabolism (liver) and excretion (kidney), along with several glands. Very low levels were found in the brain, spinal cord and in renal fat. From peak levels, a fast decline of radioactivity concentrations was observed for all organs and tissues in males and females during the whole testing period. In both sexes, concentrations fell for most organs and tissues below 5% of the maximum after one day and below the limit of quantification after seven days post administration. No significant retention of [pyridinylmethyl-^{14}C] BYI 02960 in male and female rats was found.
	ADME with [furanone-4 ^{14}C]-BYI 02960-male Wistar rats	48844143 (2011b) Acceptable/guideline Single gavage dose of 2 mg/kg bw [furanone-4-^{14}C]BYI 02960 in 0.5% aqueous Tragacanth®	[Furanone-4-14C]BYI 02960 was nearly completely absorbed since >79% and >91% of the total dose administered was detected in the urines and the organs of male and female rats, respectively. The absorption started immediately after dosing; peak plasma concentration (C_{max}) was reached approximately 1.5 hours after administration in both sexes. The distribution of the radioactivity within the body was fast. From the maximum plasma level (Cmax), the radioactivity level declined slowly down to approximately 50% of Cmax after 8 hours in both sexes and <1% of Cmax 72h after dosing. Excretion was rapid and mainly by the renal route. The major part of the dose was excreted within 24 hours after treatment. At 168 hours after administration, approximately 0.5% of the dose administered for males and approximately 0.2% for females was still detected in the body. The parent compound was metabolized to approximately 20 metabolites in total, consisting of one major (BYI 02960-OH) and six minor metabolites of an isolated and purified compound. Parent compound represented the predominant part of the radioactivity in urine but in feces the metabolite, BYI 02960-OH, was more prominent. The principal metabolic reactions of [furanone-4-^{14}C]BYI 02960 in rats were: (1) hydroxylation followed by conjugation with glucuronic acid or with sulphate; (2) cleavage of the difluoroethyl group forming BYI 02960-desdifluoroethyl; (3) cleavage of the molecule at the pyridinylmethyl bridge forming BYI 02960-difluoroethyl-amino-furanone; and (4) cleavage of molecule at the nitrogen-carbon bond next to the furanone moiety followed by further conversion to C1 and C2 compounds of the natural pool including complete degradation to carbon dioxide.

Table A.2.2. Repeated dosing, neurotoxicity, mutagenicity, and metabolism studies on Flupyradifurone.			
Guideline No.	**Study Type**	**MRID No. (Date)/Classification/ Doses**	**Results**
	[Furanone-4-^{14}C] whole body autoradiography-rat	48844144 (2011b) Acceptable/Guideline a single gavage dose of 5 mg/kg bw [furanone-4-^{14}C]BYI 02960 in 0.5% aqueous Tragacanth®.	BYI 02960 was readily absorbed from the gastrointestinal tract and distributed throughout the body immediately after administration. At 2 days after dosing, the excretion of radioactivity via urine and feces was almost completed with renal excretion as the predominant route. By 168 hours post dosing approximately 81% in males and 88% in females of the administered dose were recovered in urine and approximately 14% in males and 6% in females in the feces. Approximately 1 % (females) to 3% (males) of the dose was exhaled as 14C-carbon dioxide during a sampling period of 48 hours. In male and female rats, maximum radioactivity levels were reached for nearly all organs and tissues at one hour after administration. At this time, the values for liver, kidney, brown fat, myocardium, nearly all glandular and hormonal organs, and the olfactory bulb were higher than that in the blood. After seven days, low radioactive residues were measured in nearly all organs and tissues. No evidence for accumulation or significant retention of [furanone-4-^{14}C]BYI 02960 in male and female rats
	[Furanone-4-^{14}C] Metabolism in Organs and Tissues--rat	48844145 (2012b) Acceptable/guideline A single gavage dose of 3 mg/kg [furanone-4-^{14}C]BYI02960 in 0.5% aqueous Tragacanth® and sacrificed by exsanguination under anaesthesia at 6 hours post dosing.	Highest radioactivity levels were detected in the liver and kidney which are the main organs responsible for metabolism and urinary excretion. The residue-values for plasma and the other tissues were comparable for both sexes. In the 6 h samples of plasma, organs, and tissues, the parent compound (BYI 02960) was by far the largest component accounting for more than 72% of the total radioactive residues (TRR). For all identified metabolites, the values were less than 12% of the TRR. In the respective urine sample pools, the parent compound was the largest radioactive component (≈ 22% of the dose in males and 38% in females). The metabolism was qualitatively similar in male and female rats. The differences occurred however quantitatively. Metabolism of the parent compound to the different metabolites was significantly higher in males compared to female rats
	ADME with [Ethyl-1 ^{14}C]-BYI 02960-male Wistar rats	48844146 (2011a) Acceptable/guideline a single gavage dose of 2 mg/kg bw [Ethyl-1-^{14}C]BYI02960 in 0.5% aqueous Tragacanth®	[Ethyl-1-^{14}C]BYI02960 was nearly completely absorbed since >85% of the total dose administered was detected in the urine and the body without GIT at sacrifice. The absorption started immediately after dosing; the peak plasma concentration (C_{max}) was reached approximately 1 hour after administration. The distribution of the radioactivity within the body was fast. From the maximum plasma level (C_{max}), the radioactivity level declined slowly down to approximately 50% of C_{max} within 8 hours and to approximately 8% of C_{max} 72h after dosing. Elimination was rapid and mainly by the renal route. The major part of the dose (>87%) was excreted within 24 hours after treatment. Approximately 82% of the total administered dose was excreted in the urine and approximately 14% in the faeces. Only a negligible part of 0.2% of the total administered dose was detected in expired air. At the time of sacrifice, 72 hours after administration, a

Table A.2.2. **Repeated dosing, neurotoxicity, mutagenicity, and metabolism studies on Flupyradifurone.**			
Guideline No.	**Study Type**	**MRID No. (Date)/Classification/ Doses**	**Results**
			small proportion of approximately 3% of the total dose administered was still detected in the body without GIT. Parent compound, one major (BYI 02960-OH) and five minor metabolites were identified. The label specific metabolite BYI 02960-DFA was additionally identified (representing ≈5.77% of the administered dose). Parent compound represented the predominant part of the radioactivity in urine but in faeces samples (≈56% of the administered dose) the metabolite BYI 02960-OH was more prominent. The principal metabolic reactions of [ethyl-1-14C]BYI 02960 in rats were: (1) hydroxylation followed by conjugation with glucuronic acid; (2) cleavage of the difluoroethyl group leading to BYI 02960-DFA; and (3) cleavage of the molecule at the pyridinylmethyl bridge leading to BYI 02960-difluoroethyl-amino-furanone.
	[Ethyl-1-^{14}C] - Metabolism in organs and tissues-rat	48844147 (2012a) Acceptable/guideline a single gavage dose of 3 mg/kg bw [ethyl-1-^{14}C]BYI02960 in 0.5% aqueous Tragacanth®	The distribution of the radioactivity within the central compartments of the body (e.g. blood, liver, and kidney) was fast for both sexes. Radioactivity residues showed a distinctive preference towards the liver and kidney as the main organs responsible for metabolism and urinary excretion. Metabolism of BYI02960 was extensive. Metabolic reactions took place at least at 3 different structural positions of the test compound. The principal metabolic reactions of [ethyl-1-14C]BYI 02960 in rats were: (1) hydroxylation followed by conjugation with glucuronic acid, (2) cleavage of the difluoroethyl group leading to BYI 02960-DFA and (3) cleavage of the molecule at the pyridinylmethyl bridge leading to BYI 02960-difluoroethyl-amino-furanone. In the 24 hours samples of plasma, and organs and tissues BYI 02960-DFA was the by far largest metabolite accounting for more than 50% of the TRR. For all other identified metabolites, the values were less than 10% of the TRR. The percentage-values of the parent compound in these samples ranged from 6 to 38% of the TRR. In the respective urine sample pools, the parent compound was the largest radioactive component (approximately 48% of the dose in males and 77% in females). The metabolism was qualitatively similar in male and female rats. The differences occurred however quantitatively. Metabolism of the parent compound to the different metabolites was significantly higher in males compared to female rats.

<table>
<tr><th colspan="5">Table A.2.2. Repeated dosing, neurotoxicity, mutagenicity, and metabolism studies on Flupyradifurone.</th></tr>
<tr><th>Guideline No.</th><th>Study Type</th><th>MRID No.
(Date)/Classification/ Doses</th><th colspan="2">Results</th></tr>
<tr><td rowspan="2">870.7600
(Triple pack)</td><td>In-vivo Dermal absorption study in rats.
200 g/L Soluble concentrate formulation (SL200)</td><td>48844557 (2010)
Acceptable
Undiluted 200 g/L SL formulation, 0.625 g/L aqueous dilution, or 0.1 g/L aqueous dilution. Exposure time: 8 hours.</td><td>Using the 24 hour measuring values, the potential dermal absorptions were: 19.6%, 8.3% and 10.3% for undiluted 200/L SL formulation, 0.625 g/L aqueous dilution, and 0.1 g/L aqueous dilation, respectively.</td><td rowspan="2">Based on the 24 –hour measuring dermal absorption values from the in vivo and in-vitro dermal absorption studies with 0.1 g/L aqueous dilution , the in vivo human dermal absorption factor was estimated to be 7.42%</td></tr>
<tr><td>In-vitro dermal penetration studies with rat and human skin.
200 g/L Soluble concentrate formulation (SL200)</td><td>48844558 (2010)
Acceptable
Undiluted 200 g/L SL formulation, 0.625 g/L aqueous dilution , or 0.1 g/L aqueous dilution. Exposure time: 8 hours.</td><td>Based on 24-hour measuring interval, the dermal penetration were:
Rat skin: 0.15%, 5.67%, and 6.61% for 200 g/L concentrate, 0.625 g/L aqueous dilution, and 0.1 g/L aqueous dilution, respectively.
Human skin: 0.20% 2.01%, and 4.75% for 200 g/L concentrate, 0.625 g/L aqueous dilution, and 0.1 g/L aqueous dilution, respectively

The human DAF was derived as follows: in vivo human absorption (% absorbed) = (in vitro human % absorption × in vivo rat % absorbed) ÷ in vitro rat % absorption.</td></tr>
<tr><td colspan="5">Immunotoxicity study</td></tr>
<tr><td>870.7800</td><td>28-Day Dietary Immunotoxicity Study</td><td>48844148 (2011)
Acceptable / Guideline
0, 125, 600, 3000 ppm
0, 10, 50, 230 mg/kg/day</td><td colspan="2"><u>Systemic Toxicity</u>
NOAEL = 230 mg/kg/day
LOAEL > 230 mg/kg/day

<u>Immunotoxicity</u>
NOAEL = 230 mg/kg/day
LOAEL > 230 mg/kg/day
Immunotoxicity was not observed at the doses tested.</td></tr>
<tr><td colspan="5">Genotoxicity studies</td></tr>
<tr><td>870.5100
(84-2 a)</td><td>Mutagenic potential of <u>Salmonella typhimurium</u></td><td>48844124 (2009a)
Acceptable/guideline
TA98, TA100, TA102, TA1535, TA1537; (-/+ S9) ; 0, 16, 50, 158, 500, 1581 and 5000 µg/plate</td><td colspan="2">Negative for mutagenic activity in +/- S9 test systems up to the limit dose (5000 µg/plate).</td></tr>
<tr><td>870.5100
(84-2 a)</td><td>Reverse mutation in <u>Salmonella typimurium</u>.</td><td>48844125 (2011)
Acceptable/guideline
TA98, TA100, TA102, TA1535, TA1537 (+/-) S9
0, 3, 10, 33, 100, 333, 1000, 2500 and 5000 µg/plate for Experiment1, and 0, 33, 100, 333, 1000, 2500 and 5000 µg/plate for Experiment 2. (DMSO).</td><td colspan="2">Negative for mutagenic activity in +/- S9 test systems up to the limit dose (5000 µg/plate).</td></tr>
</table>

Table A.2.2. **Repeated dosing, neurotoxicity, mutagenicity, and metabolism studies on Flupyradifurone.**			
Guideline No.	**Study Type**	**MRID No. (Date)/Classification/ Doses**	**Results**
870.5300	*In vitro* forward gene mutation assay in mammalian cells (hamster V79 Cells) (HPRT mutation assay)	48844128 (2009) Acceptable/guideline 0, 46, 92, 184, 368, 736, 1472 and 2944 μg/mL for 5 hours (±S9) at 37°C.	Negative in the in the V79/HPRT mutation assay (+/-) S9.
870.5375 (84-2)	*In vitro* Chromosome Aberration Test with Chinese Hamster V79 Cells	48844131 (2009) Acceptable/guideline Toxicity assay, 0–3000 μg/mL (the limit dose) with a 4-hour treatment period. Seven concentrations from 0–3000 μg/mL with an 18-hour treatment period.	Negative for the induction of structural and numerical chromosome aberrations in cultured Chinese Hamster V79 cells (+/-) S9.
870. 5395	*In vivo* mouse (Crl:NMRI BR mice, males) micronucleus assy (bone marrow plychromatic erythrycytes)	48844134 (2009b) Acceptable/guidelline 0, 10, 20 and 40 mg/kg by two intra-peritoneal injections 24 hours apart.	Negative for clastogenic and aneugenic activity in the mouse bone marrow micronucleus assay.
	In vivo Micronucleus Assay in Bone Marrow Cells of the Mouse (females)	48844135 (2011) Acceptable/guideline 0, 12.5, 25 and 50 mg/kg by two intra-peritoneal injections 24 hours apart.	Negative for clastogenic and aneugenic activity in the mouse bone marrow micronucleus assay.
Toxicity Studies on Metabolites			
Difluoroacetic acid—(BCS-AA56716)			
	14-Day oral toxicity study-rat (dietary)	48844153 (2011) 0, 500, 2000, & 8000 ppm M: 0, 48, 187 & 745 mg/kg bw/ day F:0. 51, 201 & 800 mg/kg bw/ day	NOAEL = 51 mg/kg/day LOAEL = 187 mg/kg/day based on mean glucose concentration reduced by 41% in males and 48% in females (p <0.01), mean urea concentration was 25% higher in females (not statistically significant) in comparison to the controls.
	90-day oral toxicity study-rat (dietary)	48844113 (2012) Acceptable/guideline 0, 200, 1000, 6000 ppm M: 0, 12.7, 66.2, 380 mg/kg/day F:0, 15.6, 78.7, 472 mg/kg/day	NOAEL = 12.7/15.6 mg/kg/day (M/F) LOAEL = 66.2/78.8 mg/kg/day (M/F) based on a number of findings including reduced body weight approaching 10% on week 13, decreased food consumption, black foci in the glandular part of the stomach with correlated histopathology finding of focal glandular erosion/necrosis. In addition, slight decreases in hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, and hematocrit.
	Bacterial reverse mutation (*Salmonella typhimurium* strains TA98, TA100, TA102, TA1535, TA1537)	48844126 (2010a) Acceptable/guideline 0, 3, 10, 33, 100, 333, 1000, 2500 and 5000 µg/plate (+/-) S9	**Negative** for mutagenic activity *Salmonella Typhimurium*. (+/-) S9

Table A.2.2. Repeated dosing, neurotoxicity, mutagenicity, and metabolism studies on Flupyradifurone.			
Guideline No.	**Study Type**	**MRID No. (Date)/Classification/ Doses**	**Results**
	Mammalian cell gene mutation (Chinese Hamster V79 cell/HPRT)	48844129 (2010a) Acceptable/guideline 0, 30, 60, 120, 240, 480 and 960 μg/mL (+/-) S9	**Negative in (+/-) S9 V79/HPRT mutation assay.**
	In vitro cytogenetics (chromosome aberration assay in Chinese hamster V79 cells)	48844133 (2010b) Acceptable/guideline 0, 240, 480 and 960 μg/mL (+/-) S9	**Negative** for the induction of structural and numerical chromosome aberrations in cultured Chinese Hamster V79 cells (+/-) S9.
BCS-CC98193 (BYI 02960-difluoroethyl-amino-furanone)			
	28-Day oral toxicity study – rat (dietary)	48844109 (2012) Acceptable/Guideline 0, 200, 800, 3000 ppm M:0, 17, 67, 244 mg/kg/day F:0,19, 76, 256 mg/kg/day	NOAEL = 244/273 mg/kg/day (M/F) (HDT) No adverse effect was found at all tested dose levels.
	Bacterial reverse mutation *Salmonella typhimurium* strains TA98, TA100, TA102, TA1535, TA1537	48844127 (2010b) Acceptable/guideline 0, 3, 10, 33, 100, 333, 1000, 2500 and 5000 μg/plate for Experiment1, and 0, 33, 100, 333, 1000, 2500 and 5000 μg/plate for Experiment 2.In DMSO.	Negative tested up to the limit dose 5000 μg/plate (+/-) S9.
	Mammalian gene mutation (Chinese Hamster V79 Cells/HPRT)	48844130 (2011) Acceptable/guideline 0, 51.3, 102.5, 205, 410, 820 and 1640 μg/mL (+/-) S9.	Negative in the V79/HPRT mutation assay (+/-) S9
	In vitro cytogenetics (chromosome aberration assay in Chinese hamster V79 cells)	48844133 (2011a) Acceptable/guideline 0–1636 μg/mL (the limit dose)	Positiv**e (-S9)** Negative **(+S9)**
	In vivo mouse bone marrow micronucleus assay	48844136 (2011b) Acceptable/guideline 0, 125, 250 and 500 mg/kg by two intra-peritoneal injections 24 hours apart	Negative for clastogenic or aneugenic activity in the mouse bone marrow micronucleus assay.
	In vivo UDS with rat hepatocytes	48844137 (2011c) Acceptable/guideline 0, 1000 and 2000 mg/kg by a single oral gavage dose.	Negative in unscheduled DNA synthesis at up to the limit dose of 2000 mg/kg bw.
(6-chloro-3-pyridyl)methanol (IM-0)			

Table A.2.2. Repeated dosing, neurotoxicity, mutagenicity, and metabolism studies on Flupyradifurone.			
Guideline No.	**Study Type**	**MRID No. (Date)/Classification/ Doses**	**Results**
	Bacterial reverse gene mutation assay *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537, and *Escherichia coli* strain WP2*uvrA*	44988432 (1997) Acceptable/guideline 0, 313, 625, 1250, 2500 and 5000 µg/plate. (in DMSO)	Negative up to the limit dose (5000 µg/plate) with (+/-) S9.
6-chloronicotinic acid (IC-0)			
	Bacterial reverse gene mutation assay *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537, and *Escherichia coli* strain WP2*uvrA*	44988502 (1997b) Acceptable/guideline 0, 313, 625, 1250, 2500 and 5000 µg/plate. (in DMSO). (+/-) S9	Negative up to the limit dose (5000 µg/plate) with (+/-) S9.

A.3 Hazard Identification and Endpoint Selection

A. 3.1 Acute Reference Dose (aRfD) – General population including female 13+

Study Selected: Acute neurotoxicity study in rats
MRID No.: 48844138
Dose and Endpoint for Establishing aRfD: NOAEL = 35 mg/kg/day. LOAEL = 50 mg/kg/day based on increased incidences of piloerection in both sexes and pupil dilation in females on Day 1. At the next higher dose level (200 mg/kg) or above, the observed effects included lower muscle tone, rapid respiration, low arousal, tremors, myoclonic jerks, chewing, repetitive licking of lips, gait incoordination, flattened or hunched posture, dilated pupils, impaired (uncoordinated or slow) righting reflex, impaired flexor and tail pinch responses and reduced rectal temperature. Automated measures of motor activity were also reduced in both sexes, compared to controls.
Uncertainty Factor (UF): 100 (10x intraspecies, 10x interspecies); FQPA SF = 1x
Comments about Study/Endpoint/Uncertainty Factor: The acute neurotoxicity study is appropriate; the clinical sign, pupil dilatation, is one of the classical signs produced by activation of nicotinic acetylcholine receptor (nAchR) and is a single dose effect. The selected NOAEL is also protective of the effects seen in the rabbit developmental toxicity study, where increased number of dead fetuses and dead fetuses per litter were seen at 80 mg/kg/day.

$$\text{aRfD} = \frac{35 \text{ mg/kg/day}}{100} = 0.35 \text{ mg/kg/day}$$

$$\text{aPAD} = \frac{0.35 \text{ mg/kg/day}}{1} = 0.35 \text{ mg/kg/day}$$

A.3.2 Chronic Reference Dose (cRfD)

Study Selected: One year Oral Toxicity Study in Dogs
MRID No.: 48844121
Dose and Endpoint for Establishing cRfD: NOAEL = 7.8 mg/kg/day. LOAEL = 28 mg/kg/day based on skeletal muscle degeneration.
Uncertainty Factor (UF): 100 (10x intraspecies, 10x interspecies); FQPA SF = 1x
Comments about Study/Endpoint/Uncertainty Factor: The one year dog study is appropriate for both the duration and population of concern. The effect (skeletal muscle degeneration) found at the LOAEL or above is rather serious and may relate to mode of the pesticidal action (activation of nicotinic acetylcholine receptions at the neuromuscular junction) of the chemical. In addition the NOAEL (7.8 mg//kg/day) is protective of the offspring effect (decrease in F2 pup body weight) observed in the 2-generation reproduction study.

$$\text{cRfD} = \frac{7.8 \text{ mg/kg/day}}{100} = 0.078 \text{ mg/kg/day}$$

$$\text{cPAD} = \underline{0.078 \text{ mg/kg/day}} = 0.078 \text{ mg/kg/day}$$

A.3.3 Incidental Oral Exposure (Short-Term)

Selected Study: 90-Day Oral Toxicity Study in Dogs
Co-critical study: 2-Generation reproduction study in rats
MRID No.: 48844114
Dose and Endpoint for Risk Assessment: NOAEL = 12 mg/kg/day. LOAEL = 33 mg/kg/day based on skeletal muscle atrophy/degeneration

Uncertainty Factor (UF): Residential Level of Concern for MOE = 100

Comments about Study/Endpoint/Margins of Exposure: This study is appropriate for the duration of exposure. In addition, the toxicity endpoint (skeletal muscle degeneration) is rather serious and may relate to mode of the pesticidal action (activation of nicotinic acetylcholine receptions at the neuromuscular junction) of the chemical and the dog is the most sensitive species. In addition the NOAEL (12 mg//kg/day) is protective of the offspring effect (decrease in F2 pup body weight) observed in the 2-generation at 38.7 mg/kg/day in the 2-generation reproduction study. The 2-generation reproduction study is selected as a co-critical study in selection.

A.3.4 Dermal Exposure (Short-term; 1-30 Days)

Selected Study: 90-day oral toxicity study in dogs
Co-critical study: 2-Generation reproduction study in rats
MRID No.: 48844114
Dose and Endpoint for Risk Assessment: NOAEL = 12 mg/kg/day. LOAEL = 33 mg/kg/day based on skeletal muscle atrophy/degeneration decreases in body weight towards the end of the study (7-9%).

Uncertainty Factor (UF): MOE = 100

Comments about Study/Endpoint/Margins of Exposure: This study is appropriate for the duration of exposure. In addition, the toxicity endpoint (skeletal muscle degeneration) is rather serious and may relate to mode of the pesticidal action (activation of nicotinic acetylcholine receptions at the neuromuscular junction) of the chemical and the dog is the most sensitive species. In addition the NOAEL (12 mg//kg/day) is protective of the offspring effect (decrease in F2 pup body weight) observed in the 2-generation at 38.7 mg/kg/day in the 2-generation reproduction study.

Inhalation Exposure (Short- and Intermediate-Term)
Selected Study: 90-day oral toxicity study in dogs
Co-critical study: 2-generation reproduction study in rats.
MRID No.: 48844114
Dose and Endpoint for Risk Assessment: NOAEL = 12 mg/kg/day. LOAEL = 33 mg/kg/day based on skeletal muscle atrophy/degeneration.

Uncertainty Factor (UF): MOE =100

Comments about Study/Endpoint/Margins of Exposure: No route specific (inhalation) study is available. This dog oral toxicity study is appropriate for the duration of exposure. In addition, the toxicity endpoint (skeletal muscle degeneration) is rather serious and may relate to mode of the pesticidal action (activation of nicotinic acetylcholine receptions at the neuromuscular junction) of the chemical and the dog is the most sensitive species. In addition the NOAEL (12 mg//kg/day) is protective of the offspring effect (decrease in F2 pup body weight) observed in the 2-generation at 38.7 mg/kg/day in the 2-generation reproduction study.

A.4 Executive Summaries

A.4.1 Subchronic Toxicity

870.3100 90-Day Oral Toxicity - Rat

In a subchronic dietary study (MRID 48844111), BYI 02960 (99.5%; NLL 7780-44-6) was administered to six to seven week-old Wistar Rj:WI (IOPS HAN) rats in groups of 10 rats/sex/dose at 0, 100, 500, or 2500 ppm daily for 95 to 97 days (0/0, 6.0/7.6, 30.2/38.3, and 156/186 mg/kg bw/d for M/F, respectively). Two additional groups (10 rats/sex/dose) received 0 or 2500 ppm for the same treatment period, then received diet free of the test substance for an additional 30 or 31 day recovery period.

There were no test substance related effects on clinical signs or FOB parameters, unscheduled mortality, ophthalmology, or urinalysis parameters. The study also examined test substance concentrations in plasma during the last week of the study; the results indicated a linear increasing trend between plasma concentration vs. dose level administered between 100 and 500 ppm, but a sub-linear increasing trend between 100 and 2500 ppm plasma concentrations of test substance. A slight sex-specific difference in test substance plasma concentrations was noted, with higher levels observed in females (1.3–1.7× higher than males).

At 2500 ppm, decreases in mean absolute body weight and body weight gains were observed in both sexes during the treatment period. During day 8 measuring interval, the absolute body weight decrement in females reached 10%, and at day 14 the decrease was 8%. Thereafter, the decrease in body weight was below 8% and persisted until the end of the study. The slight body changes were not considered adverse in males; for females, the decrease (↓10%) reached the magnitude of being adverse at the beginning of the study. The adverse body weight effect in females might reflect higher concentrations of the test compound in females relative to males. The food consumption was consistently decreased in both males and females (↓9% to ↓29%). The increased incidence of gross and histopathological changes in the thyroid (dark color thyroid and thyroid follicular cell hypertrophy) combined with increased absolute and relative thyroid weights are considered to be adverse.

No adverse effects were found at 100 and 500 ppm.

Therefore, the NOAEL in both sexes was 500 ppm (38 mg/kg bw/day); LOAEL was 2500 ppm (156 mg/kg bw/day) based on increased incidence of thyroid follicular cell hypertrophy with associated increases of absolute and relative thyroid weights, decreased body weights in females, and decreased food consumption in both sexes.

This study is classified as fully reliable (acceptable/guideline) and satisfies guideline requirements for a subchronic oral toxicity in rats [OPPTS 870.3100; OECD 408 (1998)].

870.3100 90-Day Oral Toxicity - Mouse

In a 90-day dietary study (MRID 48844112), BYI 02960 (99.5%; NLL 7780-44-6) was administered to six week old C57BL/6J mice in groups of 10/sex/dose at 0, 100, 500, or 2500 ppm (equivalent to 0/0, 15.6/18.8, 80.7/98.2, or 407/473 mg/kg bw/d). Analysis of the plasma concentration of the test substance was conducted on blood samples of 5/sex/dose group.

Under the conditions of this study BYI 02960 did not affect mortality or produce clinical signs of toxicity. In addition, the test chemical did not produce adverse effects at 100 and 500 ppm.

In males at 2500 ppm, lower body weight gain led to terminal body weights being 10% lower than controls. While decreases in body weight gain in males may be associated with decreased absolute food consumption, particularly in study weeks 1 to 2, where up to 11% lower consumption was observed Terminal body weights were unaffected in 2500 ppm females when accounting for differences in starting body weights.

At 2500 ppm, clinical chemistry examinations showed a 30/24% (M/F, $p \leq 0.01$) decrease in serum cholesterol, 38% ($p<0.01$) increase in alkaline phosphatase (ALP) activity in male serum, and 106% increase in alanine aminotransferase (ALT) activity in female serum. Absolute and relative liver weights were increased in females at 2500 ppm. When the clinical chemistry parameter changes were considered in the context of an increased severity of diffuse centrilobular hepatocellular hypertrophy in both sexes, these findings were consistent with toxicologically adverse hepatocellular toxicity in both sexes.

Additionally at 2500 ppm, in clinical chemistry examinations there were increases of 51% in serum urea ($p \leq 0.05$) in males and a 5% decrease ($p \leq 0.05$) in serum protein in both sexes. When considered in the context of an 11% ($p<0.01$) decrease in absolute and relative (to brain weight) kidney weight, along with the absence of multifocal/diffuse cortical epithelial cell vacuolation, collectively, these changes suggest test substance related, toxicologically adverse renal toxicity in males at 2500 ppm.

The NOAEL was 500 ppm (81 mg/kg/day) for both sexes. The LOAEL was 2500 ppm (407 mg/kg/day) based on based on consistent decreases in body weight (>10%) with associated reduction in body weight gains in male, liver effects (↑ ALP and ALT, ↓ in total cholesterol, ↑ in absolute and relative liver weights, increased incidence of moderate diffuse hepatocellular hypertrophy). Kidney effects (changes in clinical chemistry parameters and loss of multifocal/diffuse cortical epithelial cell vacuolation & increases in urea).

The results of the plasma analysis showed that test substance concentrations in plasma at 90-days were higher in males than in females at all dose levels. In both sexes, a generally linear correlation between administered concentrations of test substance and plasma concentrations was observed.

This study is classified as fully reliable (acceptable/guideline) and satisfies guideline requirements for a subchronic oral toxicity in mice [OPPTS 870.3100; OECD 408].

870.3150 90-Day Oral Toxicity - Dog

In a 90-day dietary study (MRID 48844114), BYI 02960 was administered to seven to eight month old beagle dogs in groups of 4/sex/dose at dietary concentrations of 0, 400, 1200, or 3600/2400ppm (high dose reduced from 3600 ppm starting on study week 9). Dose levels were equivalent to 0/0, 12/12, 33/41, and 102[85]/107[78] mg/kg bw/d respectively.

BYI 02960 did not affect mortality, ophthalmology, or urinalysis parameters in this study.

Clinical signs were confined to the 3600 ppm dose groups, where one male and one female experienced unsteady/stiff back legs and lower back on study days 44 (both sexes) and 53 and 54 (for the male only). These findings led to reduction of the dose to 2400 ppm from study week 9 (day 56) onwards.

Over study days 0 to 14, both sexes at 3600 ppm experienced group mean body weight loss of 4/6% (M/F), respectively. Mean body weights at 3600/2400 ppm were over 10% lower than controls by study week 7 (11/14% decrease in M/F, statistically insignificant), reached a maximum difference of 14/16% ($p \leq 0.05$ in M only) lower than controls at study week 8, and partially recovered thereafter, resulting in terminal body weights 11/13% lower than controls at study week 13. Group mean body weight gains in both sexes at 1200 ppm gradually decreased from controls from study week 3 onwards, resulting in 9/7% lower body weights compared with controls at study week 13. The decreases in body weight gain as well as instances of body weight loss were at least partially accounted for decreased food consumption.

In haematology, dose- and time point-related trends were observed for decreases in RBC count, plasma haemoglobin and haematocrit compared with controls, and the findings are consistent with a treatment-related effect at 3600/2400 ppm.

In clinical chemistry, both sexes at ≥ 1200 ppm had marked increases in group mean creatine kinase (CK), aspartate aminotransferase (AST), and alanine aminotransferase activities (ALT), and at 3600/2400 ppm there were decreased serum creatinine levels and increased serum cholesterol in both sexes, and increased glucose in females. However, all findings but ALT activity in males at ≥1200 ppm had resolved by study day 84.

In terminal findings, organ weight changes were observed in 3600/2400 ppm males, with relative (to body weight) kidney weights increased by 31% ($p \leq 0.05$), absolute prostate weights increased by 67% ($p \leq 0.05$) and relative prostate weights by 88% ($p \leq 0.05$).Increased relative kidney weights (16%; not statistically significant) were also observed in females at 3600/2400 ppm, and increased absolute (14/11% in M/F, $p \leq 0.05$ in M only) and relative (28/24% in M/F, $p \leq 0.05$) liver weights were also seen at 3600/2400 ppm.

Pathology examinations reported skeletal muscle myofiber atrophy/degeneration in 2/4 males (both minimal severity) and all four females (3 minimal, 1 slight severity) at 1200 ppm, with an increase in severity at 3600/2400 ppm in males only (1 minimal, 1 slight). All four females at 3600/2400 ppm reported skeletal muscle myofiber atrophy/degeneration of minimal severity. Accumulation of brown pigment to a minimal severity was seen in hepatic Kupffer cells of 2/4 females at 3600/2400 ppm, but was absent from all other groups.

The no-observed-adverse-effect level (NOAEL) for both sexes was 400 ppm (12 mg/kg/day). The LOAEL was 1200 ppm (33 mg/kg/day), based on increased incidence of skeletal muscle myofiber atrophy/degeneration with associated increases in CK. AST, and ALT levels.

This study is classified as fully reliable (acceptable/guideline) and satisfies guideline requirements for a subchronic oral toxicity in dogs [OPPTS 870.3150; OECD 409].

870.3200 21/28-Day Dermal Toxicity – Rat

In a 28-day dermal toxicity study (MRID 48844115), BYI 02960 (96.2%) was applied to the shaved, intact dorsal skin of male and female Wistar: Crl:WI(Han) rats (10/sex/dose). The test material was moistened with deionized water and applied onto approximately 58 cm^2 shave skin for 28 daily (consecutive) applications. The rats were exposed to the test material for a minimum of 6 hours per day at 0, 50, 150 and 500 mg/kg bw/day. Parameters evaluated included body weight, body weight gain, food consumption, clinical signs, clinical pathology, ophthalmology, organ weights, and gross and microscopic pathology.

Under the conditions of this study, no effects attributable to exposure to BYI02960 were observed in body weight, body weight gain, food consumption, clinical signs, clinical pathology, ophthalmology, or gross and microscopic pathology data.

The absolute and relative liver weights at 500 mg/kg/day males were decreased by 6% and 9%, respectively, compared to control rats, with only the relative decrease obtaining statistical significance. There were no test material related clinical or gross or microscopic pathology changes to correlate this finding. **Consequently, based on the results of this study, the no-observed-adverse-effect-level (NOAEL) was 500 mg/kg bw/day (HDT) for both male and female rats.** The study report stated that the highest dose, 500 mg/kg bw, was selected after consideration of the amount of test material that could be reliably applied to the skin.

This study is considered to be fully reliable (acceptable/guideline) and to meet the data requirements for a 28-day dermal toxicity study (OPPTS 870.3200; OECD 410).

870.3465 90-Day Inhalation – Rat
The inhalation study was waived (HASPOC, 2/20/2014, TXR# 0056903)

A.4.2 Prenatal Developmental Toxicity

870.3700a Prenatal Developmental Toxicity Study - Rat
In a developmental toxicity study (MRID 48844116), groups of mated Crl:CD®(SD) female rats (23/dose group) received BYI 02960 (96.2% purity) in 0.5% aqueous methylcellulose 400 vehicle at doses of 0, 15, 50, or 150 mg/kg bw/day (10 mL/kg bw dosing volume) on gestation days (GD) 6 to 20. For dams, parameters evaluated were: body weight, body weight gain, food consumption, survival, clinical signs, reproductive outcomes, and gross pathology. Fetal parameters evaluated were: fetal body weight, incidences of dead fetuses and/or fetal resorptions, and incidences of external, visceral, head, and skeletal malformations and variations.

For dams, there were no test substance-related effects on survival, reproductive outcomes, or gross necropsy findings. The mean number of corpora lutea, implantation sites, resorptions, live fetuses, fetal weight and sex ratio were comparable across all groups and controls. An increased incidence of salivation (20/23) in 150 mg/kg bw/day animals was noted and considered a treatment-related effect. Additionally, a lower gestational body weight gain in females was noted as a treatment-related effect, with a 16% lower corrected body weight gain at 150 mg/kg bw/day compared with controls, and statistically significant decreased food consumption in the same dose group over GD 6 to 12 compared with controls. No adverse maternal effects were observed in the 50 and 15 mg/kg bw/day groups.

In fetuses, there were no test substance-related effects on the incidence of malformations or external variations. However, at 150 mg/kg bw/day, the incidence of the variations "parietal (unilateral/bilateral): incomplete ossification" and "hyoid centrum: incomplete ossification" were higher than in the control group and were outside the in-house historical control at both litter and fetal levels. These findings were indicative of a slightly delayed fetal development and considered to be test substance related. No adverse developmental effects were found in 50 and 15 mg/kg bw/day fetuses.

The maternal NOAEL was 50 mg/kg bw/day, and maternal LOAEL was 150 mg/kg bw/day, based on salivation, lower gestational body weight gain and decreased food consumption during the treatment period.

The developmental NOAEL was 50 mg/kg bw/day; developmental LOAEL was 150 mg/kg bw/day, based on increased incidences of incomplete parietal and hyoid centrum skull bone ossification indicative of delayed fetal development.

This study is fully reliable (acceptable/guideline) and satisfies the requirements for a developmental toxicity study in rats **(**OPPTS 870.3700; OECD 414; Directive 87/302/EEC Part B; MAFF 12 Nousan 8147).

870.3700b Prenatal Developmental Toxicity Study - Rabbit

In a developmental toxicity study (MRID 48844117) by oral gavage dosing, time-mated female NZW (Crl: KBL) rabbits in groups of 23/dose received BYI02960 (96.2% purity) in 0.5% aqueous methylcellulose 400 vehicle at doses of 0, 7.5, 15, or 40 mg/kg bw/d in dosing volumes of 4 mL/kg bw/d between gestation days (GD) 6–28. For the dams, the following parameters were evaluated: body weight, body weight gain, food consumption, survival, clinical signs, reproductive outcomes, liver weight and gross pathology. Foetal parameters evaluated were the following: foetal body weight, incidences of dead fetuses, and external, visceral, head, and skeletal malformations and variations.

There were no test substance-related effects on maternal clinical signs, reproductive parameters litter data endpoints, or gross necropsy findings. However, during GD 6–8, decreased corrected body weight gain and decreased food consumption were observed in 40 mg/kg bw/d maternal animals. However, the absolute body weights of the treated and the controls groups were comparable. The decreases in body weight gain and in the food consumption were marginal; these observations were considered not to be toxicologically adverse in this case. **Therefore, the maternal NOAEL was established at 40 mg/kg bw/d, based on no adverse effects were seen at the highest dose tested. When the data of this main study were considered in combination with those of the range finding study (MRID 49113601) (Attachment: Abbreviated Review of the Range Finding study), a maternal LOAEL was established at 80 mg/kg bw/d based on the markedly decrease in food consumption starting GD 6-10 and persisted at lower magnitude to the end of the study and clinical signs (no feces or few feces over several days).**

As no evidence of developmental toxicity was observed, and no evidence of an increased frequency of treatment-related, toxicologically adverse external, visceral or skeletal malformations and variations were found; **the developmental toxicity, NOAEL is 40 mg/kg bw/d, the highest dose tested in this study**. However, at 80 mg/kg bw/d in the range finding study, there was an increase in the number of dead fetuses (7 fetuses in 4 litters) relative to the controls (2 fetuses in 1 litter). This finding demonstrated an increase in the percent of dead fetuses per litter (80 mg/kg/d: 7.8% vs. Control: 1.9%). This increase was reported to be outside of the historical control range of the performing laboratory (0.74 – 6.58%). **Therefore the LOAEL for developmental toxicity could be established as 80 mg/kg bw/d.**

This study is fully reliable (acceptable/guideline) and satisfies the requirements for a developmental toxicity study in rabbits **when considered with the results from the range-finding study (**OPPTS 870.3700; OECD 414; Directive 87/302/EEC B.31; MAFF 12 Nousan 8147).

A.4.3 Reproductive Toxicity

870.3800 Reproduction and Fertility Effects - Rat

In a two-generation reproduction study (MRID 48844119), groups of Wistar [(Crl:WI) Han] rats (30/sex/group) received BYI 02960 in the diet (96.2%; BYI 02960-01-03) at concentrations of 0, 100, 500, or 1800 ppm (equivalent to 0, 6.6/7.7, 32.5/38.7, and 117/137 mg/kg bw/day for P_1–M/F premating intakes; and 0/0, 6.4/7.8, 32.0/39.6, and 122.1/143.4 mg/kg bw/day for P_2–M/F premating intakes). The test substance was solvated in acetone prior to incorporation into the diet. Parental animals received the test diet for at least 70 days before the two week mating period. Confirmed pregnant dams then continued to receive admixed diet during gestation (22 days) and lactation to weaning (21 days). During lactation, test substance concentrations were reduced by 50% to account for the corresponding increases in feed intakes of dams during this period. At weaning on LD 21, F_1 pups (30/sex/group) were randomly selected to comprise the P_2 generation and treated in the same manner as their respective P_1 generation sires and dams. Excess F_1 pups were necropsied. P_2 maternal animals were retained until weaning of the subsequent F_2 generation at LD 21.

Under the conditions of the study, BYI 02960 produced no effects on clinical signs, gross necropsy findings, reproductive organs, sperm parameters, or gestation length in both reproductive generations.

In parental observations, clear treatment-related decreases in mean body weight (↓10%) with associated reduction in body weight gain were observed at 1800 ppm in P_2 females during premating period. Decreased food consumption was noted at 1800 ppm females in both generations during the pre-mating period.

While reproductive parameters were unaffected by treatment in P_1 females, a slight decrease (-17%) in the number of estrus cycles and a slight decrease (-8%) in the total number of implantation sites were noted in 1800 ppm P_2 females, which may be associated with the decreased body weights observed at the same dose. In addition, a slight reduction in epididymal sperm count in P_1 and P_2 males and in testicular sperm count in P_2 males was observed at 1800 ppm.

In terminal observations, treatment-related histopathological changes were noted in the liver (centrilobular hepatocellular hypertrophy) in P_1 males, and accompanied by slight (+9%) increases in the absolute and relative liver weights, though these changes were considered an adaptive effect in the context of this study. While statistically significant increases in absolute and relative liver weights were also noted in other 1800 ppm animals across both generations, no other treatment-related liver histopathological findings were observed. An increase in the relative thyroid weight in both P_1 and P_2 males was not accompanied by gross or histopathological change, and the toxicological significance is uncertain.

Ovarian follicle counts in F_1 females selected as P_2 maternal animals were unaffected by treatment with the test substance.

In fetal observations, general survival parameters were unaffected by treatment in both generations. A slight decrease (-15%) in overall litter size in F_2 pups at 1800 ppm was noted, and when considered along with decreased (-8%) overall implantations in P_2 dams, suggests a slight effect on reproductive function at 1800 ppm.

Pup body weights were unaffected by treatment at 100 ppm in both generations. Treatment-related and statistically significant decreases in mean body weight (-7 to -14%) and body weight gain (-8 to -14%) were observed during the weaning period in both generations at 1800 ppm, and in the F_2 generation at 500 ppm. Terminal findings (necropsy, histopathology and organ weight analyses) did not report treatment-related effects in both generations.

Treatment-related changes in sexual maturation were limited to slight delays in vaginal patency and preputial separation at 1800 ppm in F_1 pups; these effects were considered secondary to decreased mean body weights in these animals during weaning.

The NOAEL for parental toxicity was 500 ppm (38.7 mg/kg bw/d); the LOAEL was 1800 ppm (137 mg/kg/day) based on decreased body weight (↓10%) with associated reduced body weight gains in P_1 females during the pre-mating period.

The **NOAEL for offspring toxicity was 100 ppm (7.7 mg/kg bw/day); LOAEL was 500 ppm (38.7)** based on decreased body weight (-7%) in the F_2 male and female pups.

The **NOAEL for reproductive toxicity was 500 ppm (38.7 mg/kg bw/day); LOAEL was 1800 ppm (137 mg/kg/day)** based on a 17% lower ($p \leq 0.05$) number of estrus cycles, In addition, a slight reduction in epididymal sperm count in P_1 and P_2 males and in testicular sperm count in P_2 males was observed.

This study was classified as reliable (**acceptable/guideline**) and satisfied the guideline requirements (OPPTS 870.3800; OECD N0. 416; MAFF 12 Nousan 8147) for a reproduction and fertility study.

A.4.4 Chronic Toxicity

870.4100a (870.4300) Chronic Toxicity – Rat

In a combined chronic/carcinogenicity study (MRID 48844123), Wistar Rj:WI (IOPS HAN) rats in groups of 70/sex/concentration received BYI 02960 (96.2%; 2009-000239) in the diet at concentrations of 0, 80, 400, or 2000 ppm daily for 52 weeks (10/sex/concentration; interim sacrifice) or 104 weeks (60/sex/concentration). Achieved group mean daily intakes over the entire study duration were 0/0, 3.17/4.48, 15.8/22.5, and 80.9/120 mg/kg bw/d for M/F, respectively. Following overnight fasts on study days 369 to 371 for interim sacrifice groups or study days 739 to 753 for carcinogenicity phase groups, all surviving animals were sacrificed by isoflurane inhalation.

Parameters evaluated included clinical signs, body weight, body weight gain, food consumption, test compound intakes, haematology, clinical chemistry, coagulation, urinalysis, ophthalmology, organ weights, and gross and microscopic pathology. In addition, blood samples were collected from five randomly selected animals from each group on study weeks 52 and 105, and analysed for levels of parent compound in plasma.

There was no evidence of carcinogenic potential for the test substance at the doses tested in this study. The incidence of premature mortality was unaffected by dosing.

During the first year of dosing, clinical signs were confined to the 2000 ppm dose level in the form of increased incidences of soiled fur for both sexes, alopecia (females only), and in males only, external stimuli hyper-reactivity (7% vs. 0 to 1.4% in other groups), and handling resistance (approx. 2 to 4-old increased incidence). All clinical signs had resolved by the second year of dosing with the exception of slight increased incidences of alopecia and soiled fur in males at 2000 ppm. In the absence of other clinical signs of toxicity, the increased incidences of alopecia and soiled fur were not considered toxicologically adverse findings.

Statistically significant differences in mean body weights were confined to the 2000 ppm groups in both sexes, In males, a peak decrease of -7% body weight ($p \leq 0.01$) at 2000 ppm compared with controls was noted at study week 14, with a final week 106 difference in body weight of -6% between 2000 ppm and control animals (not statistically significant). In females at 2000 ppm, mean body weights were 8% lower than controls by study week 14 ($p \leq 0.01$), with peak body weight differences of -17% between 2000 ppm and control animals at week 78 and final body weight differences of -13% terminal body weight at 2000 ppm compared with controls at study week 106 ($p \leq 0.01$). It is likely that the decreased body weight gain may be secondary to the decreased food consumption observed at 2000 ppm in females.

Ophthalmological findings at the one year examination showed an increased incidence of lens opacity in females at 2000 ppm relative to controls (14.3% vs. 4.3%). A small consistent increase in serum cholesterol in females at 2000 ppm relative to controls throughout the study was observed, but this change was not considered to be adverse. Plasma concentration analyses after both one and two years of treatment indicated a consistent relationship between increasing test substance administration and plasma levels of the test substance for both sexes, with a sub-linear relationship observed in males and an approximately linear relationship observed in females.

At both the 52-week and 104-week scheduled sacrifices, treatment-related changes in organ weights were confined to increased relative (to body weight) liver weight ($p \leq 0.01$ in both sexes) at 2000 ppm that were accompanied by liver gross and histopathological changes, including centrilobular hypertrophy and macrovacuolation in both sexes; eosinophilic/tigroid/mixed foci of hepatocellular alteration in males, and increased brown pigmentation of Kupffer cells, general hepatocellular brown pigmentation and interstitial mononuclear cell infiltrate in females.

Other treatment-related terminal findings reported in the study included lung findings at 104 weeks in 2000 ppm females, comprising of increased incidence of white foci visible at necropsy. Lung histopathology at 2000 ppm identified lesions comprised of foamy macrophages and chronic interstitial and perivascular inflammation. Additionally, increased thyroid colloid alteration in 2000 ppm males, slightly increased frequency of follicular cell hypertrophy at 2000 ppm in both sexes, and increased brown pigmentation of follicular cells in 2000 ppm females were considered treatment-related and toxicologically adverse.

Adverse effects were not found in 400 and 80 ppm test groups.

The no-observed adverse-effect level (NOAEL) in this study was 400 ppm (15.8/22.5 mg/kg bw/d for M/F respectively). The LOAEL was 2000 ppm (80.9/120 mg/kg bw/d for M/F respectively), based on a range of in-life and terminal changes in both sexes. In-life changes included decreased mean body weight with associated reduction in body weight gain (both sexes), a slightly decreased mean food consumption rate (females only), and a slightly earlier onset of lens opacity (females only) during the first year of treatment. Terminal findings considered included increased relative (to body weight) liver weights at study termination (both sexes), which were accompanied by histopathological changes in the liver (centrilobular hypertrophy and macrovacuolation in both sexes; eosinophilic/tigroid/mixed foci of hepatocellular alteration in males; increased brown pigmentation of Kupffer cells, general hepatocellular brown pigmentation and interstitial mononuclear cell infiltrate in females). Additional histopathological changes at 2000 ppm included an increased frequency in a range of effects in the thyroid (colloidal alteration in males, follicular hypertrophy in both sexes) and lungs (fomay macrophages and chronic interstitial and perivascular inflammation).

This study is classified as fully reliable (**acceptable/guideline**) and satisfies guideline requirements for a combined chronic oral toxicity/carcinogenicity study in rats [OPPTS 870.4300; OECD 453 (1981].

870.4100b Chronic Toxicity - Dog

In a 1-year dietary study (MRID 48844121), BYI 02960 (96.2%; batch 2009-000239) was administered to 5 to 6-month old beagle dogs (4/sex/dose) at concentrations of 0, 150, 300, or 1000 ppm (0/0, 4.6/4.1, 7.8/7.8, and 28.1/28.2 mg/kg bw/d for M/F, respectively) for one year. Parameters evaluated included body weight, body weight gain, food consumption, test compound intakes, clinical signs, haematology, coagulation, clinical chemistry, urinalysis, ophthalmology, organ weights, and gross and microscopic pathology. In addition, after an overnight fast blood samples were collected from 1/sex at 0 and 300 ppm animals on study day 141 and analysed for test substance concentrations in plasma.

Under the conditions of this study, there were no test substance-related effects on clinical signs, survival, haematology, coagulation, clinical chemistry, urinalysis, ophthalmology, general macroscopic findings and organ weight parameters.

Changes in body weight gain were confined to females at 1000 ppm, with an 86% lower body weight gain relative to controls in study week 1, and 17 to 66% lower relative gains over the first two 13-week intervals and the final 26 week interval of the study. This decreased body weight gain resulted in terminal body weights being 9% lower in females at this dose relative to controls. The decreased body weight gain in females at 1000 ppm during week 1 may partially be linked to a 26% lower food consumption relative to controls over the same period. The decease decrease in absolute body weight was slight and showed no statistical significance. Therefore, the changes in body weight were not considered to be adverse. In addition, group mean food consumption was unaffected when averaged across the whole one year treatment period.

Blood plasma levels of BYI 02960 in animals in the 300 ppm dosing group on study day 141 peaked at 3 hours after withdrawal of food. A slightly elevated blood plasma concentration of test substance was observed in males compared with females.

Test-substance related histopathological findings were confined to myofiber degeneration in skeletal muscle, particularly in gastrocnemius muscle at a 50% incidence and in bicep muscle at 75% incidence in both sexes receiving 1000 ppm diets. These lesions were of either minimal or slight severity (each at 1 or 2 out of a maximum severity of 5). All animals presenting with gastrocnemius muscle degeneration also presented with biceps femoris muscle lesions, giving a

total incidence for muscle histopathology of 75% in both sexes at 1000 ppm. Degeneration of the myofiber comprised of one or more of the following changes: atrophy, necrosis, and/or presence of inflammatory cells around the affected myofiber. In addition, there was a slight increase in ALT level.
The no-observed-adverse-effect level (NOAEL) was 300 ppm (7.8 mg kg bw/d for both M/F) for both sexes. The LOAEL was 1000 ppm (28.1/28.2 mg kg bw/d for M/F) for both sexes, based on increased incidence of minimal-to-slight, focal to multifocal areas of skeletal muscle degeneration in gastrocnemius and biceps femoris (75% combined incidence) in both sexes with associated slight increase in ALT level.

This study is fully reliable (acceptable/guideline) and satisfies the data requirements for a chronic toxicity study in dogs (OPPTS 870.4100; OECD 452).

870.4200b Carcinogenicity (feeding) - Mouse

In a carcinogenicity study (MRID 48844122), C57BL/6J mice received BYI 02960 (96.2%) in the diet at concentrations of 0, 70, 300, or 1500 ppm for 52 weeks (10/sex/concentration) or 78 weeks (50/sex/concentration). Achieved group mean daily intakes over the entire study duration were 0/0, 10.0/12.2, 43/53, and 224/263 mg/kg bw/d for M/F, respectively. Parameters evaluated included clinical signs, body weight, body weight gain, food consumption, test compound intakes, haematology, ophthalmology, organ weights, gross pathology (all groups) and histopathology (78-week group only). In addition, blood samples were collected and analysed for levels of parent compound at weeks 52 and 78.

There were no treatment-related effects on survival or clinical signs of toxicity across all dose levels tested. No adverse effects were observed at 70 and 300 ppm.

At 1500 ppm, treatment-related decreased mean body weights (-6%/-7% for M/F) and body weight gain (-19%/-13% for M/F) were observed compared with controls at statistically significantly levels. While food consumption in 1500 ppm animals was similar to controls, with only marginal decreases observed in females (-2–3% vs. controls), the decreased mean body weight and body weight gain suggest decreased food use efficiency, and in this context, the changes in body weight and body weight gain are considered toxicologically adverse. However, the US EPA secondary reviewer considered the changes in the body weight parameters not approaching a magnitude of being adverse. In terminal findings at 1500 ppm, increased absolute and relative liver weights in males were observed and correlated to a toxicologically adverse change in liver histopathology (increased frequency and severity of diffuse hepatocellular vacuolation). Increased incidence of small/atrophic kidneys and decreased kidney weights were seen in 1500 ppm males.

Based on the study findings, the NOAEL was 300 ppm (43/53 mg/kg bw/d for males/females respectively). The LOAEL was 1500 ppm (224/263 mg/kg bw/d for males/females respectively), based on statistically significant increases in absolute and relative liver weights, with correlative liver histopathology (diffuse hepatocellular vacuolation) and decreased kidney weights and alterations in kidney pathology in males (small/atrophic kidneys).

Under the conditions of this study, no treatment-related increases in tumor incidence were

observed at all dose levels tested.

Blood plasma analyses indicated that the concentration of test substance in plasma scaled in an approximately linear manner with increasing dietary dose at both 52 and 78 week time points. There were minor sex differences in test substance concentrations at both time points, with males presenting with slightly elevated concentrations compared with females. However, no accumulation of test substance was noted during the study.

This study is classified as fully reliable (**acceptable/guideline**) and satisfies guideline requirements for a carcinogenicity toxicity in mice [OPPTS 870.4200; OECD 451 (1981)].

A.4.6 Mutagenicity

Gene Mutation

Guideline #: 870.5100. Bacteria reverse mutation test., MRID 48844124 Acceptable/guideline	Bacteria reverse gene mutation assay using *Salmonella typhimurium* strains TA98, TA100, TA102, TA1535, TA1537 with and without an exogenous metabolic activation system (S9) with dose levels of 0, 3, 10, 33, 100, 333, 1000, 2500 and 5000 µg/plate for Experiment1, and 0, 33, 100, 333, 1000, 2500 and 5000 µg/plate for Experiment 2. The test substance was administered to the test system as a solution in dimethyl sulfoxide (DMSO). **Under the conditions of this study, BYI 02960 was tested up to the limit dose (5000 µg/plate) and was negative**

In vitro mammalian cell assay

Guideline #: 870 5300. study type: Test *In Vitro* Forward Mutation assay (V79/HPRT) MRID 48844128Accetable/guideline	In a Chinese Hamster V79 cell/HPRT mutation assay, BYI 02960 (96.2% purity) was tested in the presence and absence of an exogenous metabolic activation system (S9) at concentrations of 0, 46, 92, 184, 368, 736, 1472 and 2944 µg/mL for 5 hours (±S9) at 37°C. The highest concentration level was set based on the lack of test substance precipitation at a concentration greater than the limit dose of 10 mM. Cells were then independently subcultured for assessment of cytotoxicity (cloning efficiency) and for expression and selection of the 6-thioguanine (2-amino-6-mercaptopurine)-resistant phenotype. The test substance was dissolved in dimethyl sulfoxide (DMSO) at a maximum concentration of 300 mg/mL. Ethyl methanesulfonate (EMS) and dimethylbenzanthracene (DMBA) were used as positive controls for the non-activated and activated test systems, respectively. In the mutagenesis assay, visible precipitate was observed at the limit dose of 2944 µg/mL. However, no excessive cytotoxicity was observed at any concentration tested, and no concentration- and treatment-related increases in mutant frequency were observed. **BYI 02960 was negative in the non-activated and S9-activated test systems in the V79/HPRT mutation assay.**

In vivo cytogenetic

Guideline 8705385. ***In Vivo* micronucleus assay in mouse bone marrow-** MRID MRID 48844134 Acceptable /guideline	In the mouse micronucleus assay, male Crl:NMRI BR mice (5/dose level) were administered BYI 02960 at doses of 0, 10, 20 and 40 mg/kg by two intra-peritoneal injections 24 hours apart, Concurrent control groups were administered corn oil (the vehicle (negative) control), or 20 mg/kg of cyclophosphamide (positive control). All animals were sacrificed 24 hours after the second i.p. injection. Bone marrow smears were prepared immediately after the sacrifices. In-life observations included clinical signs. Two thousand PCEs per animal were evaluated for micronuclei. In the main study, there were no deaths, though treatment-related toxicity was observed, including apathy, roughened fur, weight loss, sternal recumbency, spasm, periodic stretching of the body and difficulty breathing. No evidence of a cytotoxic effect on the bone marrow cells was observed, while the positive and vehicle controls induced the expected response. No statistically significant increases in micronucleated PCE frequency were observed in any evaluated test substance-treated group of animals. **Under the conditions of this study, BYI 02960 was neither clastogenic nor aneugenic in the mouse bone marrow micronucleus assay.**

A.4.7 Neurotoxicity

870.6200 Acute Neurotoxicity Screening Battery

In an acute neurotoxicity study (MRID 48844138), Wistar (Rj:WI (IOPS HAN)) rats in groups of 12/sex/dose received BYI 02960 (96.2%; 2009-000239) at 0, 50, 200, or 800 mg/kg bw/day as single oral gavage dose in methylcellulose 400 (0.5% v/v) at 10 mL/kg bw final dosing volumes. A follow up cohort of 12 females/dose received 0, 20, or 35 mg/kg bw/day oral gavage doses.

Neurobehavioral parameters examined in the first cohort consisted of motor activity and functional observational battery (FOB) assessments at 2 hours post dosing and on Days 7 and 14 after treatment, along with neuropathological examinations of the peripheral and central nervous systems at study termination.

There were two instances of unscheduled mortality in females at 800 mg/kg bw/day, with animals found dead on study Days 1 (day of dosing) and Day 5, respectively. Both mortalities were test substance related. Clinical signs prior to death in the animal found dead on study day 1 consisted of piloerection, low muscle tone and arousal, rapid respiration, tremors, myoclonic jerks, convulsions, dilated pupils, absence of pupil and flexor reflexes and uncoordinated or slow surface righting reflex.

Effects on body weight gain were confined to 40/46% (M/F) lower mean body weight gains at 800 mg/kg bw/day in study week 1 relative to controls that subsequently resolved such that by study day 14 there were no differences in group mean body weight.

Changes in FOB and activity parameters were confined to study day 1 only, with no treatment-related findings being present on study days 7 or 14.

At 50 mg/kg bw/day, increased incidences of piloerection in males and females (8/12 for M and 7/12 for F, vs. 4/12 for both M and F controls) and of dilated pupils in females (6/12, vs. 1/12 for controls) were observed on study day 1.

At 200 mg/kg bw/day/day, piloerection, dilated pupils, rapid respiration, lower muscle tone, low arousal, repetitive licking of lips, decreased rearing, exaggerated flexor reflexes, gait incoordination and flattened body posture, and higher incidence of tremors were seen in both sexes. In addition, males from the 200 mg/kg bw/day/day dose group exhibited myoclonic jerks and absence of movement, and were also cold to touch, while a higher incidence of walking on tiptoes was observed in females at this dose. Automated measures of motor activity were reduced during the first 10-min interval of the session in both sexes.

At 800 mg/kg bw/day/day, piloerection, lower muscle tone, rapid respiration, low arousal, tremors, myoclonic jerks, chewing, repetitive licking of lips, gait incoordination, flattened or hunched posture, dilated pupils, impaired (uncoordinated or slow) righting reflex, impaired flexor and tail pinch responses and reduced rectal temperature were observed. Automated measures of motor activity were also reduced in both sexes.

In the follow-up study, the animals at 20 and 35 mg/kg showed no treatment-related effects in all the parameters examined.

No gross or microscopic test substance-related morphological changes were seen in the nervous system tissues.

The NOAEL in this acute neurotoxicity study is 35 mg/kg bw/day/day; LOAEL is 50 mg/kg bw/day/day based on increased incidences of piloerection in both sexes and increased incidence of pupil dilation in females on study day 1.

This study is fully reliable (acceptable/guideline) and satisfies the data requirements for an acute neurotoxicity study (OPPTS 870.6200; OECD 424).

870.6200 Subchronic Neurotoxicity Screening Battery

In a subchronic neurotoxicity feeding study (MRID 48844139), seven-to-eight week old Wistar Rj:WI (IOPS HAN) rats in groups of 12/sex/dose received BYI 02960 (96.2%; 2009-000239) in the diet at concentrations of 0, 100, 500, and 2500 ppm (0/0, 5.7/6.9, 29.4/34.8, or 143/173 mg/kg bw/day for M/F) for 90 days. The following parameters were evaluated: body weights, body weight gain, food consumption, clinical signs, detailed physical examination, ophthalmology, and gross pathology. A neurobehavioral test battery consisting of motor activity and functional observational battery (FOB) assessments was conducted on all animals prior to BYI 02960 dosing (baseline) and during study weeks 2, 4, 8, and 13 or 14, depending on sacrifice schedule. On test days 92 and 93, 6 rats/sex/group were perfused *in situ* with fixative. The peripheral and central nervous systems and selected muscle tissues from perfused control and high dose groups were prepared for histological evaluation.

Under the conditions of the study, there were no test substance-related effects on the following parameters: mortality, ophthalmology, neurobehavioral parameters (FOB and motor activity), or gross and microscopic morphology of the nervous system in either male or female rats of any dose groups.

There was a decrease in absolute body weight in males and females at 2500 ppm reaching 9% at week 1 for females and at weeks 4 and 8 for males. The magnitude of reduced body weight did not persist or approach the level of being adverse. Associated mean body weight gains were also decreased for both sexes at 2500 ppm relative to controls from study week 1 onwards.

There were decreases in food consumptions in 2500 ppm males and female (↓18/29% (M/F) $p \leq 0.01$) over study week 1, which partially recovered over the study to reach a 9/4% (M/F) lower consumption relative to controls on study week 13.

In this 90-day neurotoxicity study with dietary administration, flupyradifurone did not produce neurotoxicity at any dose levels tested. The no-observed-adverse-effect level (NOAEL) was 500 ppm (29.4/34.8 mg/kg bw/day; M/F); LOAEL was 2500 ppm (143/147 mg/kg bw/day; M/F) based on decreased food consumption with associated slight decrease in absolute body weight.

This study is classified as fully reliable (acceptable/guideline) and meets the guideline requirements of subchronic neurotoxicity study (U.S. EPA OPPTS 870.6200; OECD 424; and MAFF Japan Nousan 8147).

870.6300 Developmental Neurotoxicity Study

In a developmental neurotoxicity study (MRID 48844140), groups of time-mated 12-week old female Wistar Han CRL:WI (HAN) (30/dose group) received acetone-solvated BYI 02960 (96.2%; 2009-000239) in the diet at concentrations of 0, 120, 500, or 1200 ppm (0, 10.3, 42.4, or 102 mg/kg bw/day) from gestation day (GD) 6 to lactation day (LD) 21. For dams, the following parameters were evaluated: body weight, body weight gain, food consumption, mortality, clinical signs, detailed physical examination, FOB examination (GD 13 and 20 and LD 11 and 21), and reproductive outcomes. For pups, neurobehavioral evaluations including learning tasks (passive avoidance and the water maze test), motor activities, and FOB parameters were evaluated throughout the post-natal period. Additional pup parameters evaluated included body weight, food consumption, ophthalmology, sexual maturation, brain weights, gross necropsy, and neural and muscle tissue histopathological and morphometric analyses.

Under the conditions of this study, for dams, there were no test substance-related effects on maternal clinical signs, FOB parameters, mortality, or reproductive outcomes. For offspring, there were no test substance related effects on clinical signs, mortality, acquisition and retention parameters for the passive avoidance and water maze tasks, sexual maturation, surface righting, pupil reflex or other ophthalmology parameters, necropsy findings, organ weights, macroscopic or histological brain morphometry, or brain or peripheral nerve histopathology.

During gestation, a decrease in body weight was seen (↓7%) in 1200 ppm dams and associated decreases in body weight gain were present. At lactation period a decrease of (4% to 6 %) in body weight was also found in1200 ppm dams. A slight decrease in food consumption was found in the dames at various times during the gestation and lactation periods (ranging from 1% to 8%). However, these changes were slight and not considered as adverse.

For pups, a non-statistically significant increase in both motor and locomotor activity was seen in males at 1200 ppm on PND 13 relative to concurrent controls. On PND 60, startle amplitude for all 50 trials was statistically significantly ($p \leq 0.05$) increased by approx. 2-fold in females at 1200 ppm relative to controls.

There was no evidence of treatment-related changes in brain morphometry or peripheral nerve histopathology.

Under the conditions of this study, the maternal NOAEL was established at 1200 ppm (102 mg/kg/day) based on no adverse effects were found in the dams at the highest dose tested.

The offspring NOAEL was 500 ppm (42.4 mg/kg/day); LOAEL was 1200 ppm (102 mg/kg/day) based on statistically significant persistent increased in startle response amplitude.

This study is reliable (acceptable/guideline) and satisfies the requirements for a developmental neurotoxicity study in rats **(**OPPTS 870.6300; OECD 426).

A.4.8 Metabolism

870.7485 Metabolism – Rat

A. Pyridinylmethyl-^{14}C

In a toxicokinetic and metabolism study (MRID 48844141), groups of 4 Wistar rats per sex per dose were administered by oral gavage a single dose of 2 or 200 mg/kg bw [Pyridinylmethyl-^{14}C]BYI02960 in 0.5% aqueous Tragacanth® and sacrificed by exsanguination under anaesthesia at 72 hours post dosing. An additional group of 4 male Wistar rats were administered by i.v. a single dose of [Pyridinylmethyl-^{14}C]BYI02960 (2 mg/kg bw) in the same vehicle and sacrificed at the same time post dosing. The test compound was radiolabeled with ^{14}C in the pyridinylmethyl bridge of the molecule. The metabolism and radioactivity which included the test compound and metabolites was determined in urine and faecal samples collected for the time range between dosing and sacrifice. Additionally, radioactivity in plasma micro samples was determined over the study period (17 time points). Total radioactivity was determined in excreta and in organs and tissues collected at sacrifice. Samples were analysed, and parent compound and metabolites identified, by radiochromatographic (HPLC, TLC) and spectroscopic (LC/MS) methods.

Mean total radioactivity was nearly quantitative since approximately 91 to 103% of the administered dose was found in the excreta and in the bodies of animals at sacrifice.

[Pyridinylmethyl-^{14}C]BYI 02960 was nearly completely absorbed after oral administration, which was demonstrated by the high factor of bioavailability (F = 0.93) calculated from the plasma data of low dose tests after oral and i.v. administration, and that approximately 76 to 90% of the administered radioactivity were detected in the urine and in the bodies without GIT at sacrifice of male and female rats. The absorption started immediately after dosing as could be seen from the quick increase of radioactivity in plasma micro samples, with the peak plasma concentration (C_{max}) reached approximately 1 hour after administration in the low dose tests and within approximately 2 to 4 hours in the high dose tests.

The distribution of the radioactivity within the body was fast. From the maximum plasma level (C_{max}), the radioactivity level declined slowly down to approximately 50% of C_{max} after 4 – 8 hours in the low dose tests and after 8 – 24 hours in the high dose tests and down to low values around the LOQ in the low dose tests and to approximately 0.5% of C_{max} in the high dose tests by study termination (72 hours).

Excretion was rapid, mainly by the renal route and essentially complete by 72 hours post dosing. Female rats exhibited slightly higher renal excretion rates of approximately 86% and 90% of the administered dose compared to approximately 76% of the dose in males. The major part of the dose detected in urine (>84%) was excreted within 24 hours after treatment and was ongoing up to 72 hours. Faecal excretion accounted for approximately 23 – 26% of the total administered in males, and 7 – 10% in females. At the time of sacrifice, 72 hours after administration, the radioactive residues in organs and tissues were low, and only trace amounts of approx. <0.1 – 0.3% of the total administered dose was detected in the body and in the GIT. Most of the residues of the low dose tests were lower than 0.01 mg/kg sample. The highest concentrations of the low dose tests, but also at a low level of approximately ≤0.018 mg/kg sample were detected in blood cells, the GIT and in the eyes of female rats. The residues of the low and high dose tests were nearly proportional to the dose.

Parent compound, three major (BYI 02960-OH, BYI 02960-6-CNA and BYI 02960-hippuric acid) and five minor metabolites were isolated from urine and four of them identified by spectroscopic methods (LC-MS and 1H-NMR and 2D-NMR), HPLC and/or TLC co-chromatography or comparison. Identification rates were high in excreta, and amounted to 83% to 94% of the total administered radioactivity. Parent compound represented the predominant part of the radioactivity in urine of male and female rats. In faeces samples of male rats, the metabolite BYI 02960-OH was more prominent than the parent compound. Two metabolites, BYI 02960-6-CNA and BYI 02960-hippuric acid were also prominent metabolites in male rats but not in females. In total further 19 unknown metabolites were characterised by their chromatographic behaviour. All of them were detected at trace amounts of approximately <0.1% to 0.9% of the dose. The metabolic profiles in urine and faeces were very similar for both sexes but male rats exhibited a higher rate of metabolite formation compared to female animals. The metabolic transformation of BYI 02960 was principally oxidative and took place at least at 3 different structural positions of the test compound.

The principal metabolic reactions of [pyridinylmethyl-14C]BYI 02960 in rats were: (1) hydroxylation followed by conjugation with glucuronic acid to or with sulphate; (2) cleavage of the difluoroethyl group forming BYI 02960-des-difluoroethyl; and cleavage of the molecule at the pyridinylmethyl bridge forming BYI 02960-6-CNA, which was further conjugated with glycine to BYI 02960-hippuric acid.

The results of the toxicokinetic and metabolism study were in good accordance with those obtained in other studies performed with different radiolabels: [Ethyl-1-^{14}C]BYI 02960 (Weber, 2011a; Study No. M1824567-3, Koester, 2012a; Study No. M1824575-2) and [Furanone-4-

^{14}C]BYI 02960 (Weber, 2011b; Study No.M1824560-6, Koester, 2012a; Study No. M1824574-1, Koester, 2011b, Study No. M1821760-5).

This study is fully reliable (acceptable/guideline) and satisfies the study requirements of a metabolism study (U.S. EPA 870.7485; OECD Section 4 Part 417 and Annex to Directive 87/302/EEC, Part B, Toxicokinetic; JMAFF 12 Nousan 8147).

B. furanone-4-^{14}C

In a toxicokinetic and metabolism study (MRID 48844143), a group of 4 male and 4 female Wistar rats were administered by oral gavage a single dose of 2 mg/kg bw [furanone-4-^{14}C]BYI 02960 in 0.5% aqueous Tragacanth® and sacrificed by exsanguination under anaesthesia at 168 hours post dosing. The test compound was radiolabeled with ^{14}C in the C4-position of the furanone ring of the molecule. The metabolism and radioactivity which included the test compound and metabolites was determined in urine and faecal samples collected for the time range between dosing and sacrifice. Additionally, radioactivity in plasma micro samples was determined over the study period (23 time points). Total radioactivity was determined in excreta and in organs and tissues collected at sacrifice. Samples were analysed, and parent compound and metabolites identified, by radiochromatographic (HPLC, TLC) and spectroscopic (LCMS) methods.

Mean total radioactivity recovery was nearly quantitative since approximately 96% and 102% of the administered dose were found in the excreta and bodies of males and females respectively at sacrifice.

[Furanone-4-14C]BYI 02960 was nearly completely absorbed since >79% and >91% of the total dose administered was detected in the urines and the bodies without GIT at sacrifice of male and female rats respectively. The absorption started immediately after dosing as could be seen from the quick increase of radioactivity in plasma micro samples, with the peak plasma concentration (C_{max}) was reached approximately 1.5 hours after administration in both sexes.

The distribution of the radioactivity within the body was fast. From the maximum plasma level (C_{max}), the radioactivity level declined slowly down to approximately 50% of C_{max} after 8 hours in both sexes and <1% of C_{max} 72h after dosing.

Excretion was rapid and mainly by the renal route. Approximately 79% of the total dose administered was found the urine of male rats and approximately 91% in the urine of female rats. The major part of the dose was excreted within 24 hours after treatment, for male and female rats. At the time of sacrifice, 168 hours after administration, a small proportion of approximately 0.5% of the dose administered for males and approximately 0.2% for females were still detected in the body without GIT.

The parent compound was moderately metabolised to approximately 20 metabolites in total, consisting of one major (BYI 02960-OH) and six minor metabolites of an isolated and purified compound. Identification rates were >84% of the total dose administered in male rats and >95% in females. Another approximate 8% of the dose in males and 4% in females were characterised by their chromatographic behaviour but not identified. All metabolites accounting for >1% of the dose administered were identified except a polar metabolite fraction accounting for 5.30% in males and 2.45% in females. It is considered that this polar fraction is most likely represented by biomolecules. Parent compound represented the predominant part of the radioactivity in urine but in faeces samples the metabolite BYI 02960-OH was more prominent.

Overall, male rats showed a higher rate of metabolism with only approximately 55% of unchanged parent compound found in excreta whereas 76% of unchanged BYI 02960 was found in the excreta of female rats, though the metabolic patterns were very similar in males and females.

The principal metabolic reactions of [furanone-4-^{14}C]BYI 02960 in rats were: (1) hydroxylation followed by conjugation with glucuronic acid or with sulphate; (2) cleavage of the difluoroethyl group forming BYI 02960-desdifluoroethyl; (3) cleavage of the molecule at the pyridinylmethyl bridge forming BYI 02960-difluoroethyl-amino-furanone; and (4) cleavage of molecule at the nitrogen-carbon bond next to the furanone moiety followed by further conversion to C1 and C2 compounds of the natural pool including complete degradation to carbon dioxide.

Male rats exhibited a higher proportion of the polar metabolite fraction and higher residues in the body at the time of sacrifice, and also exhibited a higher proportion of radioactivity in exhaled air in a study with [pyridinylmethyl-^{14}C]BYI 02960 (Koester 2011a). All these observations taken together suggest that the furanone-4-^{14}C radiolabel is not completely stable and that a small part of the dose obviously underwent extensive biotransformation to C1- and C2-fragments that resulted in an incorporation of radioactivity into biomolecules, in particular in male rats.

The results of these metabolism investigations are in good accordance with those obtained from the corresponding organ metabolism rat study with [furanone-4-^{14}C]BYI 02960 (Koester, 2012b).

This study is fully reliable (acceptable/guideline) and satisfies the study requirements of a metabolism study (U.S. EPA 870.7485; OECD Section 4 Part 417 and Annex to Directive 87/302/EEC, Part B, Toxicokinetic; JMAFF 12 Nousan 8147).

C. Ethyl-1-^{14}C

In a toxicokinetic and metabolism study (MRID 48844146**)**, a group of 4 male Wistar rats were administered by oral gavage a single dose of 2 mg/kg bw [Ethyl-1-^{14}C]BYI02960 in 0.5% aqueous Tragacanth® and sacrificed by exsanguination under anaesthesia at 72 hours post dosing. The test compound was radiolabeled with ^{14}C in the C1-position of the ethyl side chain of the molecule. The metabolism and radioactivity which included the test compound and metabolites was determined in urine and faecal samples collected for the time range between dosing and sacrifice. Additionally, radioactivity in plasma micro samples was determined over the study period (23 time points). Total radioactivity was determined in excreta (including expired air) and in organs and tissues collected at sacrifice. Samples were analysed, and parent compound and metabolites identified, by radiochromatographic (HPLC, TLC) and spectroscopic (LCMS) methods.

Mean total radioactivity recovery was nearly quantitative since approximately 100% of the administered dose was found in the excreta and bodies of males at sacrifice.

[Ethyl-1-^{14}C]BYI02960 was nearly completely absorbed since >85% of the total dose administered was detected in the urine and the body without GIT at sacrifice. The absorption started immediately after dosing as could be seen from the quick increase of radioactivity in plasma micro samples, with the peak plasma concentration (C_{max}) was reached approximately 1 hour after administration.

The distribution of the radioactivity within the body was fast. From the maximum plasma level (C_{max}), the radioactivity level declined slowly down to approximately 50% of C_{max} within 8 hours and to approximately 8% of C_{max} 72h after dosing.

Excretion was rapid and mainly by the renal route. Approximately 82% of the total administered dose was excreted in the urine and approximately 14% in the faeces. Only a negligible part of 0.2% of the total administered dose was detected in expired air. The major part of the dose (>87%) was excreted within 24 hours after treatment, though excretion was ongoing in the time range between 24 and 72 hours the time of sacrifice. In particular, the major part of the metabolite BYI 02960-DFA was excreted on day 2 and day 3. At the time of sacrifice, 72 hours after administration, a small proportion of approximately 3% of the total dose administered was still detected in the body without GIT. The residue was highest in plasma with 0.158 mg/kg sample. For most other organs and tissues, levels were in the range between 0.05 and 0.1 mg/kg sample.

Parent compound, one major (BYI 02960-OH) and five minor metabolites were identified by HPLC and/or TLC co-chromatography or comparison. The label specific metabolite BYI 02960-DFA was additionally identified by high resolution LC/MS of the isolated compound. Identification rates were >95% of the total radioactivity in urine and >85% of the total radioactivity in faeces. Parent compound represented the predominant part of the radioactivity in urine but in faeces samples the metabolite BYI 02960-OH was more prominent. Approximately 92% of the total dose administered was identified in excreta. Another approximate 3% of the dose corresponding to 6 unknown metabolites were characterised by their chromatographic behaviour. All metabolites representing >1% of the dose administered have been identified.

The principal metabolic reactions of [ethyl-1-14C]BYI 02960 in rats were: (1) hydroxylation followed by conjugation with glucuronic acid; (2) cleavage of the difluoroethyl group leading to BYI 02960-DFA; and (3) cleavage of the molecule at the pyridinylmethyl bridge leading to BYI 02960-difluoroethyl-amino-furanone.

The results of the metabolism investigations are in good accordance with those obtained from the corresponding organ metabolism rat study with [ethyl-1-14C]BYI 02960 (Koester, 2012a).

This study is fully reliable (acceptable/guideline) and satisfies the study requirements of a metabolism study (U.S. EPA 870.7485; OECD Section 4 Part 417 and Annex to Directive 87/302/EEC, Part B, Toxicokinetic; JMAFF 12 Nousan 8147).

870.7600 Dermal Absorption – Rat

Dermal absorption study with technical grade active ingredient was not conducted. Triple pack dermal penetration studies were conducted with the SL formulation.

A. In vivo dermal absorption with SL formulation

In an *in vivo* dermal absorption study with a [pyridinylmethyl-^{14}C]-BYI02960 200g/L soluble concentrate (SL) formulation, 7 to 9 week-old male Wistar Rj: WI (IOPS HAN) rats in groups of 4/concentration/timepoint (MRID 48844557) over four sacrifice timepoints of 8, 24, 72, or 168 hours received either the undiluted 200 g/L SL formulation, or 0.625 g/L or 0.1 g/L aqueous dilutions for eight hours. Absorption was followed using [^{14}C]-BYI02960, which was uniformly blended into the formulations prior to application. Animals were lightly anaesthetised by an unspecified method and two plastic 'protective saddles' were secured to define the application site for the test substance The formulated products were then applied dose to a 2 x 6 cm^2 shaved area of dorsal skin as two aliquots of 60 µL (total of 120 µL) to each animal in the 12 groups (N = 4/group), and the exposed skin area and protective saddles were covered in perforated plastic as a semi-occluded cover not touching the skin, and held in place over the saddles with surgical tape (~3 x 4 cm). After eight hours, covers, saddles, and tape were removed and wiped down by swabs and distilled water. The application sites were swabbed with 1% v/v Tween 80 in PBS until no more radioactivity was detected. If necessary, the treated skin was shaved with the shavings being retained for analysis. The skin was then tape stripped until the epidermis appeared shiny. The 8 hour sampling group animals were sacrificed, while animals retained for the subsequent timepoints received new protective saddles and covers.

Urine, feces, and cage wash samples were collected individually at 0 to 8, 8 to 24, and 24-hour intervals thereafter up to the time of final sacrifice. At sacrifice, animals were subjected to terminal anesthesia by isoflurane, and exsanguinated *via* cardiac puncture. Application site skin, surrounding skin (within 1 cm perimeter, distant skin, and cardiac blood were collected, and along with skin swabs, tape strips, covers, saddle, and tape were retained for analysis of radioactivity by LSC using a Packard 1900 TR counter.
Non-absorbed dose was regarded to consist of radiolabel in dressings, surface tape strips (first two strips), and fur. Radiolabel in urine, feces, cage washes, non-treated skin and carcass was regarded as being directly absorbed. Radiolabel in stratum corneum, and skin, including surrounding skin were regarded as being potentially absorbable.

For the 200 g/L neat product, the mean total absorbable fractions were 21.78, 19.63, 17.00, and 19.18% of the applied dose for the 8, 24, 72, and 168 hour groups, respectively. Of these totals, the directly absorbed component was 2.27, 3.88, 4.39, and 8.14% of total applied dose, respectively. The test substance readily distributed to the surrounding skin, reaching 15.16% of total applied dose at 8 hours, and steadily falling to reach 7.69% of total applied dose by 168 hours. The fraction in the non-treated skin reached a maximum of 2.71% of applied dose at 72 hours, falling to 2.3% of applied dose at 168 hours. The proportion in the stratum corneum varied over time, being 1.05% at 8 hours, reaching a maximum of 4.14% of total applied dose at 24 hours, falling to 0.71% of applied dose at 72 hours, and increasing to 1.34% at 168 hours. The urine was the predominant route of excretion, containing a mean total of 2.18% of applied dose at 168 hours, while faeces contained a mean total of 0.94%. Mean total radiolabel recovery ranged from 101.1 to 113.4% of that applied dose for the 8, 24, 72, and 168 hour sacrifice groups respectively.

For the 0.625 g/L diluted product, the mean total absorbable fractions were 9.26, 8.28, 9.66, and 5.53% for the 8, 24, 72, and 168 hour exposure groups, respectively. Of these totals, the directly absorbed component was 2.21, 1.31, 2.18, and 2.24% of total applied dose, respectively. In contrast to the 200 g/L undiluted formulation, distribution to the surrounding skin was minimal, being only 0.307% of total applied dose at 8 hours, 0.345% at 24 hours and rising to 0.577% at 72 hours, and falling to reach 0.154% of total applied dose by 168 hours. The proportion in the non-treated skin was also far lower than that obtained with the 200 g/L formulation, reaching a maximum of 0.473% of applied dose at 72 hours, and falling to 0.198% of applied dose at 168 hours. The proportion in the stratum corneum was 4.86% at 8 hours and 5.96% at 24 hours, reaching a maximum at 72 hours of 6.41% of applied dose, and falling to 2.71% at 168 hours. The urine was the predominant route of excretion, containing a mean total of 1.10% of applied dose at 168 hours, while faeces contained a mean total of 0.3%. Mean total radiolabel recovery was 99.84, 99.36, 92.30, and 95.59% of total applied dose at the 8, 24, 72, and 168 hour sacrifice groups, respectively.

For the 0.1 g/L diluted product, the mean total absorbable fractions were 16.64, 10.32, 18.20, and 20.57% for the 8, 24, 72, and 168 hour exposure groups, respectively. Of these totals, the directly absorbed component was 4.32, 2.78, 5.28, and 8.12% of total applied dose, respectively. Similar to the 0.625 g/L formulation and in contrast to the 200 g/L formulation, distribution to the surrounding skin was low, being 1.53% of total applied dose at 8 hours, 0.410% at 24 hours, 0.400% at 72 hours, and rising slightly to 0.734% of total applied dose by 168 hours. The proportion in the non-treated skin was between the relatively low levels for the 0.625 g/L formulation and the high levels of the 200 g/L formulations, with a maximum of 1.551% at 8 hours, and falling to 0.794% of applied dose at 168 hours. The proportion in the stratum corneum was 8.74% at 8 hours and 6.26% at 24 hours, and as with the other concentrations, maximum levels were reached at 72 hours, at 11.69% of applied dose, and falling to slightly to 10.37% at 168 hours. The relative level of total applied dose in the stratum corneum at 168 hours was therefore 3.8-fold and 7.7-fold higher than those obtained with the 0.625 g/L and 200 g/L formulations, respectively. The urine was again the predominant route of excretion, containing a mean total of 3.00% of applied dose at 168 hours, while faeces contained a mean total of 0.443% for this timepoint. Mean total radiolabel recovery was 100.5, 95.8, 102.9, and 95.6% of total applied dose at the 8, 24, 72, and 168 hour sacrifice groups, respectively.

The last available layers of stratum corneum (tape strips 12 or 9) for the animals with the highest absorption values in each of the three 168 hour concentration groups all contained radiolabel, albeit at levels 32 to 64% lower than that on the first (surface) tape strips. When considered with the observed urinary excretion of radiolabel at 168 hour study termination, this finding demonstrated that dermal absorption of applied test material was potentially continuing up to and including the 168 hour timepoint.

The study authors stated that as a conservative estimate, the amount of BYI 02960 potentially absorbable following an 8-hour exposure ranged from 17.0 to 21.8% for the 200 g/L neat product, 5.54% to 9.66% for the 0.625 g/L intermediate dilution, and from 10.3% to 20.6% for the highly diluted 0.1 g/L formulation, based on group mean values.

The evaluator has considered that, due to the basis of high intragroup variability (standard deviation exceeding 25% of the mean), individuals in each group with the highest levels of dermal absorption were considered to be more representative of potential intraspecies variation compared to group means. On an individual animal basis, the highest absorptions of test substance were 29.9, 9.38, and 23.9% for the concentrate, 0.625 g/L, and 0.1 g/L dilutions, respectively.

In summary, following an 8-hour *in vivo* dermal exposure to [pyridinylmethyl-^{14}C]-BYI02960 200g/L SL formulation and dilutions, the maximal absorbable dose was 29.9, 9.38, and 23.9% for 200 g/L (neat), 0.625 g/L, and 0.1 g/L dilutions, respectively. The dermal absorption data from both *in vivo* and *in vitro* dermal absorption studies were used to estimate the *in vivo* dermal absorption factor for humans; the estimated factors were 42.1, 3.32 and 17.2% for BYI02960 200g/L SL concentrate, 0.625 g/L, and 0.1 g/L dilutions, respectively.

This study is reliable (acceptable) and meets the data requirements for an *in vivo* dermal absorption study (OECD TG 427 [2004]).

B. In vitro dermal penetration study with rat and human skin

The dermal penetration of a BYI02960 200g/L soluble concentrate (SL) formulation was tested *in vitro* using rat (dorsal) and human (abdominal) skin mounted in a glass flow-through diffusion cell system with an exposure area of 1 cm² maintained at 32±2ºC (MRID 48844558). The test substance was applied as either the undiluted 200 g/L SL formulation, or as 0.625 g/L or 0.1 g/L aqueous dilutions. Penetration and absorption were followed using [pyridinylmethyl-^{14}C]-BYI02960, which was uniformly blended into the formulations prior to application.
The formulated products were applied at a rate of 10 µL/cm² to 2 groups of 6 skins per dose level per species with the exception of the 0.625 g/L groups which had only 5 skins for humans and 4 for rats. The achieved concentrations of BYI02960 applied per area of skin was approximately 1800 to 2000, 4.5 to 5.0, and 0.9 to 1.1 µg/cm² for the 200, 0.625 and 0.1 g/L formulations, respectively. The formulation concentrations and application rates were designed to mimic potential field-use exposures. The applied formulation remained in contact with the skins for 8 hours. Serial receptor fluid samples (2×50 µL) were collected hourly for the 24 hour duration of the study. The volume of receptor fluid was maintained by the replacement with a volume of fresh receptor fluid, equal to the total aliquot volume. At 8 hours, the skin surfaces of all groups were washed with sponge swabs and freshly prepared 1% v/v Tween 80 in phosphate buffered saline. At 24 hours, the skin samples were swabbed again, and stripped using Monaderm adhesive tape to remove non-absorbed surface test material (first two strips) and stratum corneum (strips three until a shiny appearance had been reached, indicating complete removal). Stripping involved applying the tape for five seconds before removing the strip against the direction of hair growth.

For the 200 g/L formulation, mean total recovery was 106.1 and 105.5% of that applied for humans and rats, respectively. As a percentage of total applied dose, the potentially absorbable fraction (receptor fluid plus tape-stripped skin) over 24 hours was 0.204 and 0.145% for human and rat skin, respectively. The total absorbable dose was therefore approx. 1.4-fold greater for human skin than for rat skin. Of the potentially absorbable fraction, directly absorbed dose (receptor fluid and receptor fluid terminal) only comprised 0.016±0.029% and 0.071±0.071% of the total applied for human and rat skin, respectively. Stratum corneum contained just over half

(0.103±0.120%) of the total absorbable fraction in humans, and just over a third (0.055±0.075%) of the total absorbable for rats. Washing the skin at eight hours removed >105% of the applied dose for both species, while tape strips one and two at 24 hours removed 0.128 and 0.132% of the applied dose for human and rat skin, respectively.

For the 0.625 g/L formulation, mean total recovery was 100.3 and 96.4% of that applied for humans and rats, respectively. As a percentage of total applied dose, the potentially absorbable fraction (receptor fluid plus tape-stripped skin) over 24 hours was 2.008 and 5.667% for human and rat skin, respectively. The total absorbable dose was therefore approx. 2.5-fold greater for rat skin than for human skin. As was found for the concentrate formulation, directly absorbed dose (receptor fluid and receptor fluid terminal) was a minor contributor to the potentially absorbable total, being 0.392±0.344% and 1.075±0.330% for human and rat skin, respectively. Stratum corneum again contained just over half of the total absorbable fraction for both humans (1.149±0.534%) and rats (2.852±3.832%). Washing the skin at eight hours removed a mean of 97% and 85.5% of the applied dose for human and rat skin samples, respectively. Tape strips one and two at 24 hours removed 0.492 and 2.137% of the applied dose for human and rat skin, respectively.

For the 0.1 g/L formulation, mean total recovery was 106.1 and 105.5% of that applied for humans and rats, respectively. As a percentage of total applied dose, the potentially absorbable fraction (receptor fluid plus tape-stripped skin) over 24 hours was 4.753±2.963% and 6.607±2.796% for human and rat skin, respectively. The extent of interspecies difference at this concentration was therefore similar in magnitude to that for the concentrate, but in reverse direction, being only 1.4-fold higher for rat skin than for human skin. As was found for the two higher concentration levels, directly absorbed dose (receptor fluid and receptor fluid terminal) was a minor contributor to the potentially absorbable total, being 0.646±0.482% and 1.105±0.436% for human and rat skin, respectively. Stratum corneum again contained just over half of the total absorbable fraction for humans (2.998±1.828%) but was even higher for rats, comprising approx. two-thirds (4.409±2.893%) of the total. Washing the skin at eight hours removed a mean of 89.4% and 85.5% of the applied dose for human and rat skin samples, respectively. Tape strips one and two at 24 hours removed 0.99% and 5.86% of the applied dose for human and rat skin, respectively.

As penetration into the receptor chamber remained ongoing at the 24 hour termination point of the study for the majority of rat and human skin samples for the three formulation concentrations, test substance remaining in the stratum corneum were considered to be potentially absorbable.

Group mean values were used in the calculations of absorbable dose. Although standard deviations for the potentially absorbable fractions in all groups ranged from 42% (rat 0.1 g/L sample) to 106% (human 200 g/L sample) of the means, the variations were considered likely to be outliers arising from experimental variation/errors rather than representations of true biological variation.

Under the conditions of this *in vitro* dermal absorption study, the study author calculated the mean total potentially absorbable values in humans/rat skin samples, respectively, over 24 hours to be 0.20/0.15% for the 200 g/L formulation, 2.0/5.7% for the 0.625 g/L formulation, and 4.8/6.6% for the 0.1 g/L formulation. The evaluator agreed with the study author's conclusions.

The results obtained in this study, using an *in vitro* flow-through diffusion cell system, demonstrate that penetration and absorption of BYI02960 from the 200 g/L SL formulation was relatively equivalent to within 30 to 40% ranges in rat and human skin when applied as the undiluted concentrate or highly diluted (0.1 g/L) formulations, but that dermal absorption was nearly 3-fold higher in rats for the intermediate dilution (0.625 g/L).

The *in vitro* dermal absorption data on isolated rat and human skin in combination with the *in vivo* rat dermal absorption data were used by the primary study evaluator to estimate the *in vivo* human dermal absorption factor; the factors were 42.1%, 3.32%, and 17.2% for the concentrate, intermediate, and highly diluted formulation, respectively. ***However, US EPA secondary reviewer does not agree with the conclusion concerning the human dermal absorption factor because there are no data for the exposure duration beyond 24 hours in the in-vitro human and rat skin studies. Therefore, the US EPA determines that the appropriate estimate for the potential human dermal absorption factor to be 7.42 % based on the data on the 24-hour exposure period and most dilute administered concentration (0.1 g/l).***

This study is reliable (Acceptable) and fulfils the requirements of the OECD guideline for *in vitro* dermal absorption studies in rats and humans (OECD 428 (2004)).

A.4.9 Immunotoxicity

870.7800 Immunotoxicity

In an immunotoxicity study (MRID 48844148), BYI 02960 (96.2% a.i. batch# 2009-000239) was administered to seven week old female Wistar, Rj:WI (IOPS HAN) rats in groups of 10/dose at concentrations of 0, 125, 600, or 3000 ppm (0, 10, 50, or 230 mg/kg bw/d) for 30 days. A positive control group consisting of 10 female Wistar, Rj:WI (IOPS HAN) rats received oral gavage doses of 3.5 mg/kg bw/d cyclophosphamide at 5 mL/kg bw dosing volumes for 28 days.

On Day 26, the test animals were immunized with an injection of sheep red blood cells (SRBC). On study Day 30, blood samples were collected from the test animals and serum samples were assayed for their concentration of SRBC-specific IgM antibodies to provide a quantitative assessment of humoral immune response by ELISA. Additional parameters that were evaluated include mortality, clinical signs of toxicity, body weight, body weight gain, food consumption, selected organ weights (*i.e*. spleen, and thymus), and macroscopic examination of all major organs, tissues and body cavities.

There were no observable test substance related clinical signs, and premature mortality was confined to euthanasia of one animal at 600 ppm due to forelimb automutilation on study day 8. As this was unaccompanied by other necropsy findings, it was considered unrelated to the test substance.

Overall group mean body weight gains at 3000 ppm over study days 1 to 29 were 23% lower than that in controls ($p<0.05$), resulting in 6% lower mean terminal body weight than controls without statistical significance ($p > 0.05$). Decreases in food consumption of ≤ 34% (week 1) relative to controls were seen at 3000 ppm throughout the study period and were likely linked to changes observed in body weight gain.

Necropsy findings in negative control and test substance groups were unremarkable, whereas atrophied and/or small (5 or 6/10 animals) spleens were observed in cyclophosphamide-dosed positive control animals.

While there was a dose-related decreasing trend in absolute spleen weights relative to controls in treated animals (2%, 4% and 6% decreases at 125, 600 and 3000 ppm respectively), relative (to body weight) spleen weights were essentially unchanged at 3000 ppm (+1% increase). Similarly, absolute thymus weights at 3000 ppm were decreased by 4% relative to controls, but relative (to body weight) thyroid weights were unaffected. Positive control animals had 32 to 34% ($p \leq 0.01$) decreases in mean absolute and relative spleen weights, and 27 to 28% ($p \leq 0.01$) decreases in absolute and relative thymus weights, respectively.

The SRBC-specific IgM ELISA data showed a 55% increase from controls at 125 ppm, 15% decrease at 600 ppm, and an 18% decrease at 3000 ppm, with no findings being statistically significant ($p > 0.05$). Based on the lack of dose dependency and absence of statistical significance, overall there were no indications of test substance immunosuppressive potential up to and including the highest dose tested of 3000 ppm (~230 mg/kg bw/d). The positive control performed as expected, with a 93% decrease ($p \leq 0.01$) in anti-SRBC IgM antibody concentrations.

The immunotoxicity NOAEL is the highest dose tested of 3000 ppm (230 mg/kg bw/d), based on an absence of test substance related immunotoxicity findings at this dose.

This study is fully reliable (acceptable/guideline) and satisfies the guideline requirements (OPPTS 870.7800) for an immunotoxicity study in rats.

A.4.9 Special/Other Studies

90- day oral toxicity with DFA (metabolite)

In a 90-day dietary study (MRID 48844113), BCS-AA56716 (97.1%; batch BCOO5984-5-8) was administered to Wistar [Rj:WI (IOPS HAN)] rats (10/sex/dose) at concentrations of 0, 200, 1000, or 6000 ppm (0/0, 12.7/15.6, 66.2/78.7, or 380/472 mg/kg bw/d, respectively). BCS-AA56716 (difluoroacetic acid) is a plant and soil metabolite of BYI02960.

Parameters evaluated included body weight, body weight gain, food consumption, clinical signs, Functional Observational Battery parameters, exploratory locomotor activity, haematology, clinical chemistry, urinalysis, ophthalmology, organ weights, gross and microscopic pathology.

Under the conditions of this study BCS-AA56716 did not produced test substance-related effects on survival, clinical signs of toxicity, functional observational battery observations, ophthalmological observations, or organ weights.

In males at 1000 ppm, mean body weight by study day 8 was 4% lower than controls, 9% ($p \leq 0.01$) lower than controls by study day 29, and terminal body weights were 12% ($p \leq 0.01$) lower than controls at study day 92. Lower mean body weight and decreased body weight gain were also noted at 6000 ppm, with a mean body weight 4% lower than controls by study day 29, 6% lower by study day 57, with no further decreases through to study termination (all values were not statistically significant).

In females at 1000 ppm, mean body weight was 5% lower than controls at study day 57, and were 4% lower than controls by study day 92 (no statistical significance observed). Lower mean body weights during the treatment period were also observed at 6000 ppm in females, with a mean body weight 6% ($p \leq 0.05$) lower than controls at study day 29, 7% ($p \leq 0.05$) lower at study day 57 ($p \leq 0.05$), and 9% ($p \leq 0.01$) lower at study day 92.

Decreased body weight gains in both sexes at 1000 and 6000 ppm was accompanied by corresponding decreases in absolute (g/d) food consumption from study day 4 onwards (earliest time point examined).

In hematology observations, a 9% lower hemoglobin, 6% lower mean corpuscular volume, and 8% lower mean corpuscular hemoglobin were noted in 1000 ppm females relative to controls,. These findings all displayed poor dose dependency, with similar decreases reported at 6000 ppm. .

In clinical chemistry observations, Serum glucose concentrations and serum bilirubin were decreased across all dose levels compared with controls; however, noting the direction of change for the reported effects (decreases, rather than increases), the effects were not considered toxicologically adverse.

A range of urinalysis parameters at ≥ 1000 ppm (including urinary volume, ketone levels and urinary pH) were considered to be treatment-related, but unlikely to be toxicologically significant given the lack of histopathology and clinical pathology changes.

Test substance related findings at gross necropsy were confined to black foci in the stomach gland of both sexes at 1000 ppm (10/20% incidence for M/F) and 6000 ppm (30%/20% incidence for M/F). The finding was associated at the histopathological level with focal glandular erosion/necrosis in the stomach, and considered to be toxicologically adverse.

The NOAEL was 200 ppm for both sexes (12.7/15.6 mg/kg bw/d for M/F). The LOAEL was 1000 ppm (66.2/78.7 mg/kg bw/d for M/F), based on decreased body weight gains in males, resulting in 12% lower terminal body weights relative to controls ($p \leq 0.01$), associated decreases in food consumption, black foci in the glandular part of the stomach (10/20% incidence for M/F) for both sexes that correlated histopathologically with focal glandular erosion/necrosis, and (in females only) statistically significant ($p \leq 0.01$) decreases in plasma haemoglobin (-9%), mean corpuscular volume (-6%), mean corpuscular haemoglobin (-8%) and hematocrit (-7%).

This study is classified as fully reliable (acceptable/guideline) and satisfies guideline requirements for a subchronic oral toxicity in rats [OPPTS 870.3100; OECD 408 (1998)].

A.5 Flupyradifurone: Summary of NOAEL/LOAEL (with BW ¾ scaling for human equivalent dose)

With the initial glance, the toxicity data on flupyradifurone appear to indicate that the dog is more sensitive than the other testing animals. However, with BW ¾ scaling for human equivalent dose calculation, the results reveal that the dog and rat have similar sensitivity to the effects of flupyradifurone as indicated in the table below.

Table A.5: Flupyradifurone Summary of NOAEL/LOAEL (with BW ¾ scaling for human equivalent dose)

	NOAEL (mg/kg)		LOAEL (mg/kg)	
Study	**Test Animal**	**Human Equivalent Dose**	**Test Animal**	**Human Equivalent Dose**
28-day oral –rats (gavage)	**75**	18	200	48
28-day oral tox.-rats (dietary)	36		385	
28-day oral tox.-mice (dietary)	166/199 (M/F) (HDT			
28-day oral tox. dogs (diet) (2 dogs/sex/dose)	62	40	118	75.52
90-day oral tox.—dogs	**12**	**7.68**	**33**	**21.12**
90-day oral toxicity –rats (diet)	38	9.12	156	37.44
90-day oral toxicity –mouse (diet)	81		407	
28-day Dermal tox.-rats	500 (HDT)			
Chronic oral toxicity study in dogs. (1-year; diet)	**7.8**	**4.00**	**28**	**17.92**
Combined chronic/ carcinogenicity study in rats.	**15.8 / 22.5 (M/F)**	**3.8/5.4**	**81/ 120 (M/F)** (No compound related ↑tumor incidence)	**19.44/28.8**
Carcinogenicity study in mice	43		224 (No compound related ↑tumor incidence)	
Developmental toxicity - rabbit. (gavage)	Mat- 40		Mat 80	
	Dev-40		Dev-80	
Developmental toxicity –rat (gavage)	Mat- 50 Dev-150		Mat- 150 Dev-150	36 36
2-Generation reproduction study in rats	Parental-38.7 (HDT) Reprod-38.7 **Offspring 7.7**	**Offspring: 1.85**	Parental 137 Reprod-137 **Offspring-38.7**	**Offspring: 9.29**
Acute neurotoxicity in rats. (gavage)	35		50	
Subchronic neurotoxicity study in rats.	34.8		143	

Table A.5: Flupyradifurone Summary of NOAEL/LOAEL (with BW ¾ scaling for human equivalent dose)				
	NOAEL (mg/kg)		**LOAEL (mg/kg)**	
Study	**Test Animal**	**Human Equivalent Dose**	**Test Animal**	**Human Equivalent Dose**
Developmental neurotoxicity study in rats.	Maternal -102 (HDT) Offspring-42		Offspring-102	
28-Day Dietary Immunotoxicity Study	230 (HDT) No systemic or Immunotoxicity was see			

Appendix B. Metabolism Summary Table

Table B. Overall Summary of Characterization and Identification of Radioactive Residues in Tomato, Potato, Apple, Cotton, and Rice Following Application of [Furanone-4-14C] BYI 02960 and [Pyridinylmethyl-^{14}C] BYI 02960 at Rates and PHIs Reflective of the Proposed Uses

Compound[1]	Tomato (drench)		Potato (seed treatment)		Apple (foliar)		Cotton Lint (foliar)		Rice (foliar)	
	TRRs = 0.130P /0.096F ppm		TRRs =0.076P /0.078F ppm		TRRs = 0.545P /1.286F ppm		TRRs=8.846P/4.993F ppm		TRRs=0.620P/0.659F	
	% TRR	ppm	% TRR	ppm	% TRR	ppm	%TRR	Ppm	%TRR	ppm
BYI 02960	24/36	0.031/0.034	40/40	0.031/0.031	86/74	0.467/0.946	73/70	6.46/3.51	75/57	0.467/0.373
6-CNA	13.2/	0.017/	22/	0.016/	1.5/	0.008/	0.4/	0.031/	3.1/	0.019/
CHMP-di-glyc	37.1/	0.048/	4.4/	0.003/						
CHMP-glyc	5.1/	0.007/	3.7/0.003		0.9/	0.005/				
CHMP	3.3/	0.004/	3.9/	0.003/	0.8/	0.004/				
OH-glyc	3.4/5.5	0.004/0.005	6.7/6.6	0.005/0.005	1.7/1.1	0.009/0.014				
Glucose/ carbohydrate	/28	/0.026			/14	/0.182			/3.6	/0.023
Difluoroethyl-amino-furanone	/10	/0.01	/4.2	/0.003	/0.2	/0.003				
Acetic acid-glyc					0.8/0.5	0.004/0.007			0.6/0.4	0.003/0.003
Acetic acid					1.1/0.7	0.006/0.009			7.8/6.1	0.048/0.040
AMCP-difluroethanamine					4.1/	0.023				
OH					1.0/0.8	0.005/0.01			0.4/	0.002/
Glyoxylic acid							0.2/0.2	0.015/0.009	0.4/	0.003/
OH-glyc/acetic acid							14.6/13.9	1.30/0.694		
Bromo/chloro							1.6/1.6	0.140/0.078	1.5/1.7	0.009/0.011
Total identified	86/79	0.111/0.075	80/50	0.061/0.039	98/91	0.53/1.17	90/86	7.94/4.29	89/68	0.552/0.450
Total characterized	12/4.3	0.016/0.004	9.3/12.4	0.007/0.01	0.5/0.1	0.002/0.002	9.5/11	0.837/0.530	7.4/17.2	0.045/0.113
Total extractable	98/85		93/67		99/92		99/97	8.77/4.82	96/86	0.597/0.564
Unextractable (PES)	1.5/15		6.6/33		1.3/8.1		0.8/3.4	0.073/0.170	2.7/12.8	0.017/0.085
[Difluoroacetic acid]	[87[2]]	[0.175[1]]								

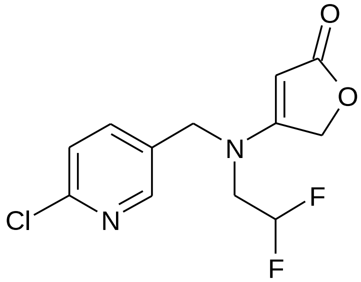
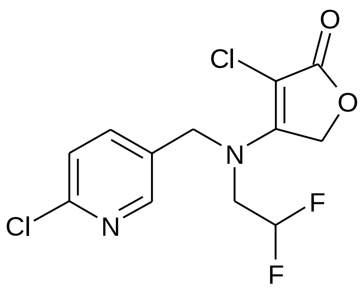
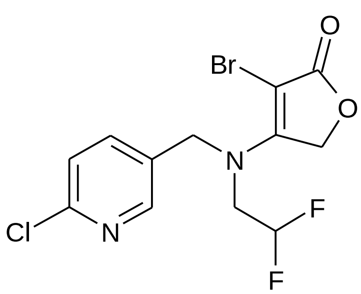
[1] See Table C.1 for names and structures.

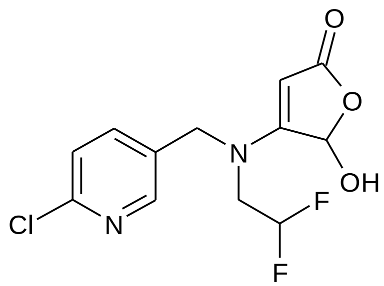
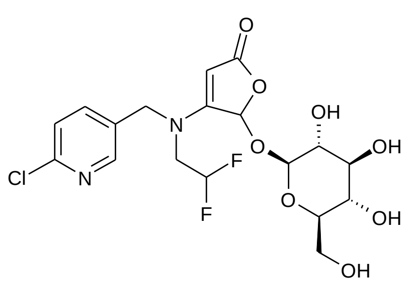
[2] [1-ethyl-^{14}C] BYI 02960. Conducted only with tomato.-

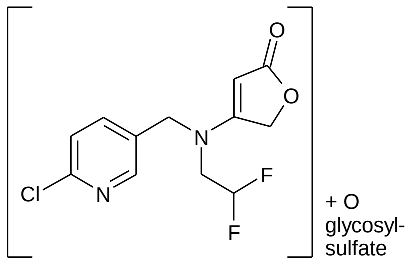
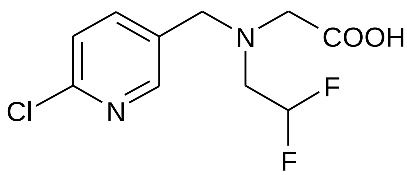
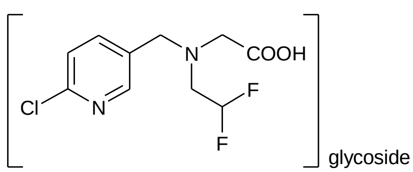
Appendix C. Physical/Chemical Properties and Metabolites

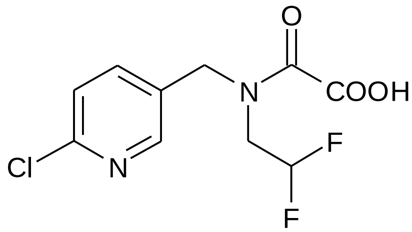
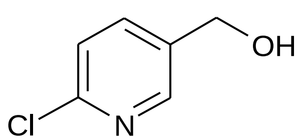
Table C.1. Physicochemical Properties of the Flupyradifurone (99.4% Purity)		
Parameter	Value	Reference (MRID/BCS Study)
Molecular weight (g/mole)	288.68	MRID 48843601 M-434475-01-1
Melting point/range (°C)	69.0	MRID 48843630 M-367370-01-2
pH	6.6 at 24º C	MRID 488436626 M-412128-01-2
Density (g/cm^3)	1.43 g/ml at 20º C	MRID 48843642 M-412635-01-2
Water solubility (g/L at 20°C)	3.2	MRID 48843643 M-204285-01-2
Solvent solubility (g/L at 20°C)	Methanol >250 n-Heptane 0.0005 Toluene 3.7 Dichloromethane >250>25 Acetone 0 Ethyl acetate >250 Dimethyl sulfoxide >250	MRID 48843656 M-414064-01-2
Vapor pressure (Pa)	9.1×10^{-7} at 20ºC 1.7×10^{-7} at 25ºC 2.6×10^{-7} at 50ºC	MRID 48843650 M-309853-01-3
Dissociation constant (pK_a)	No dissociation occurs in aqueous solutions in the pH range between 1 and 12.	MRID 48843636 M-418626-091-2
Octanol/water partition coefficient Log(K_{OW})	1.2 (pH 4 – 9)	MRID 48843639 M-414485-01-2

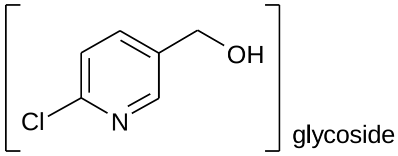
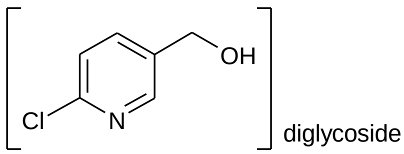
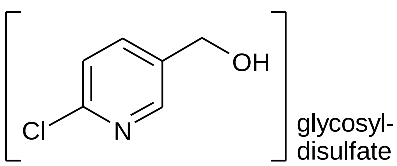
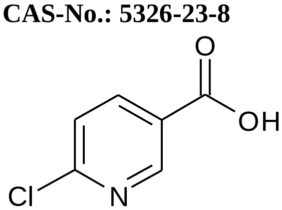
Table C.2. Tabular Summary of Flupyradifurone and Its Metabolites and Degradates.			
Chemical Name (other names in parenthesis) and Structure	**Matrix**	**Percent TRR (PPM)**	
		Matrices - Major Residue (>10%TRR)	**Matrices - Minor Residue (<10%TRR)**
Parent Flupyradifurone **BYI 02960** 4-[[(6-chloropyridin-3-yl)methyl] (2,2-difluoroethyl) amino]furan -2(5H)-one (IUPAC) 2(5H)-furanone, 4-[[(6-chloro-3-pyridinyl)methyl](2,2-difluoroethyl) amino]- (CAS) CAS-No.: 951659-40-8	Tomato	24P (0.031) 36F (0.034)	
	Potato	40P (0.031) 40F (0.031)	
	Apple	86P (0.47) 74F (0. 95)	
	Cotton	73P (6.5) 70 F (3.5)	
	Rice grain	75P (0.47) 57F (0.37)	
	CRC Wheat Grain (29 d)		8.3P (0.02) 0.4F (0.004)
	CRC Swiss Chard (29 d)	46P (0.69) 43 F (0.37)	

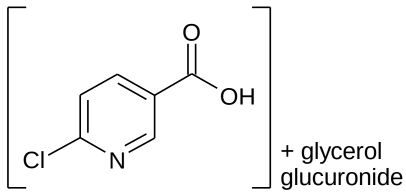
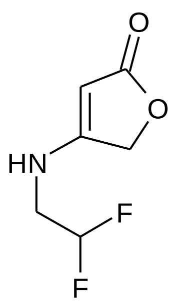
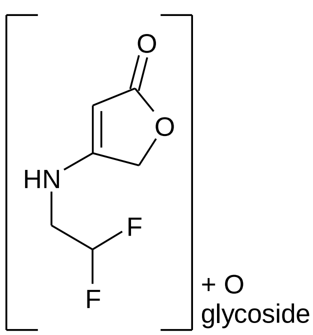
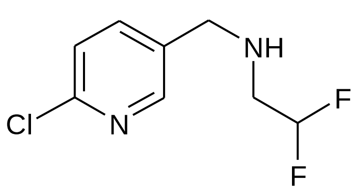
	CRC Turnip Leaf (29 d)	62P (0.51) 64 F (0.44)	
	CRC Turnip Root (29 d)	58P (0.04) 56F (0.04)	
	Ruminant milk	89P (0.16) 24F (0.25)	
	Ruminant muscle	98P(0.35) 88F (0.48)	
	Ruminant fat	99P (0.10) 80F (0.21)	
	Ruminant kidney	35P (0.65) 50F (0.74)	
	Ruminant liver	85 P (1.0) 60F (1.0)	
	Poultry egg	20P (0.017) 2.3F (0.013)	
	Poultry muscle	14F (0.005)	9.8P (0.007)
	Poultry fat	15P (0.003)	
	Poultry liver		0.9P (0.004) 0.5F (0.01)
	Rat Excreta	40-77 TDA	
BYI 02960 Chloro (Co-elutes with Bromo) 3-chloro-4-{[(6-chloropyridin-3-yl) methyl](2,2-difluoroethyl)amino} furan-2(5*H*)-one  **BYI 02960 bromo** (co-elutes with chloro) 3-bromo-4-{[(6-chloropyridin-3-yl) methyl](2,2-difluoroethyl)amino} furan-2(5*H*)-one 	Cotton		1.6P (0.14) 1.6F (0.078)
	Rice		0.4P (0.003)
	CRC Turnip root (29-296 d)		1.4-2.5P (0.001) 1.3-2.5F (0.06-0.001)
	CRC Swiss chard (29-296 d)		0.4P (0.04) 0.4-0.6F (0.003-0.001
	CRC Turnip leaves (29-296)		1.3-1.6P (0.001-0.004) 1.1-1.8F (0.007-0.002)
	Water		

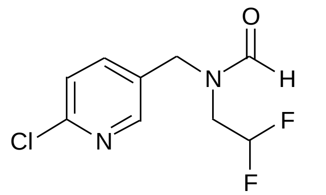
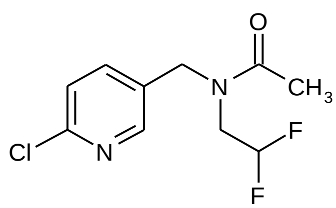
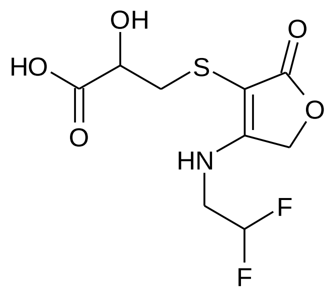
BYI 02960 OH 4-{[(6-chloropyridin-3-yl)methyl] (2,2-difluoroethyl)amino} -5-hydroxyfuran-2(5*H*)-one 	Apple		1.0P (0.005) 0.8F (0.01)
	Rice		0.4P (0.002)
	CFC Wheat grain (29d)	10P (0.018)	2.3F (0.011)
	CFC Swiss chard (29d)		1.6 P(0.023) 1.9F (0.02)
	CFC Turnip root (29d)		0.5P (0.001) 0.4F (0.001)
	CFC Turnip top(29d)		1.4P (0.011) 1.7F (0.012)
	Ruminant liver	16P (0.30) 15F (0.22)	
	Ruminant muscle		1.8F (0.01)
	Ruminant kidney		2.9F (0.008)
	Poultry eggs	18P (0.015)	2.3F (0.013)
	Poultry muscle		8.1P (0.006) 2.4F (0.004)
	Poultry fat		5.5P (0.001)
	Poultry liver		1.5 (0.007) 0.8F (0.018)
	Rat excreta	13-29 TDA	
BYI 02960 OH glyc 3-{[(6-chloropyridin-3-yl)methyl] (2,2-difluoroethyl)amino}- 5-oxo-2,5-dihydrofuran-2-yl beta- D-glucopyranoside 	Tomato		3.4P (0.004) 5.5F (0.005)
	Potato		6.7P (0.005) 6.6F (0.005)
	Apple		1.7P (0.0090 1.1F (0.014)
	CFC Wheat grain (29-296d)		5.0P (0.009) 2.1F (0.002)
	CFC Swiss chard (29-296d)	11-28P (0.16-0.036) 13-21F (0.12-0.033)	
	CFC Turnip leaf (29-296d)	10-12F (0.02-0.09)	9.4-11P (0.02-0.08)
	CFC Turnip root (29-296d)		2.5-3.8P (0.001-0.002) 2.1-3.1F (0.001)
BYI 02960-OH-glyc-SA (isomer 1) And BYI 02960-OH-glyc-SA (isomer 2)	CRC Swiss chard (29-296d)		1.7-9.2P (0.02-0.04) 4.8-6.7F (0.01-0.05)
	CRC Turnip leaf (29d)		2.3P (0.02)

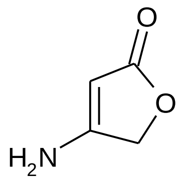
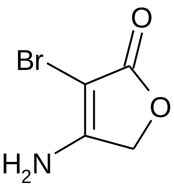
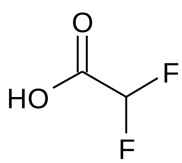
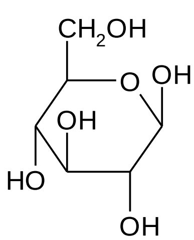
			
BYI 02960 acetic acid N-[(6-chloropyridin-3-yl)methyl]-*N*-(2,2-difluoroethyl)glycine 	Apple		1.1P (0.006) 0.7F ((0.009)
	Rice		7.8P (0.048) 6.1F (0.040)
	CRC Wheat grain (29-296d)		1.8P (0.002) 1.0F (0.002)
	CRC Swiss chard (29-296d)		0.6-0.9F (0.001-0.005)
	CRC Turnip leaf (29-296d)		1.1-1.3F (0.001-0.008)
	CRC Turnip root (29-296d)		0.2-0.3F (0.001)
	Rat		
	Water		
BYI 02960-acetic acid-glyc 	Apple		0.8P (0.004) 0.5F (0.007)
	Rice		0.6P (0.003) 0.4F (0.003)
	CRC Swiss chard (29-296d)		3.0P (0.013) 0.2-1.6F (0.001-0.01)
	CRC Turnip leaf (29d)		0.4P (0.003) 0.5-3.5F (0.001-0.02)

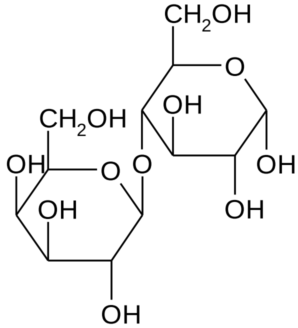
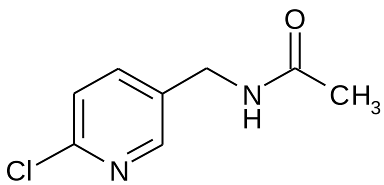
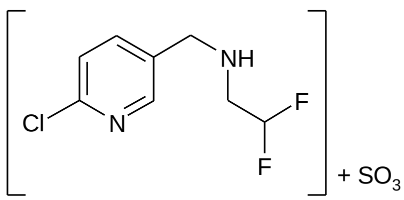
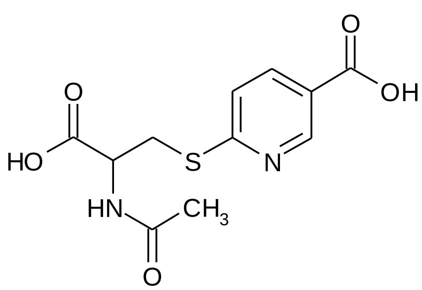
BYI 02960 glyoxylic acid N-(6-chloropyridin-3-ylmethyl)-*N*-(2,2-difluoroethyl)oxamic acid 	Cotton		0.2P (0.015) 0.2F (0.009)
	Rice		0.4P (0.002)
	CRC Wheat grain (29d) (15% wheat straw, forage, hay)		6.0P (0.011)
	CRC Swiss chard (29d)		2.6P (0.039) 4.7F (0.041)
	CRC Turnip leaf (29d)		2.6P (0.021) 6.6F (0.045)
	CRC Turnip root (29d)	12F (0.009)	8.6P (0.006)
BYI 02960 CHMP **6-chloropyridin-3-ylmethanol (IUPAC)** **3-pyridinemethanol, 6-chloro- (CAS)** **CAS-No.: 21543-49-7** 	Tomato		3.3P (0.004)
	Potato		3.9P (0.003)
	Apple		0.8P (0.004)
	CRC Turnip root (29d)		4.1P (0.003)
BYI 02960 CHMP glyc	Tomato		5.1P (0.007))
	Potato		3.7P,(0.003)
	Apple		0.9P (0.005)
	CRC Swiss chard (29d)		5.4P (0.080)
	CRC Turnip leaf (29-296d)		4.5-5.9P (0.01-0.04)

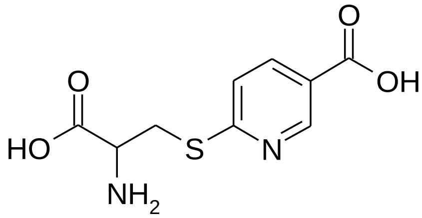
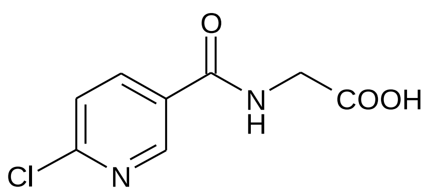
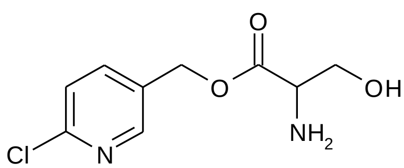
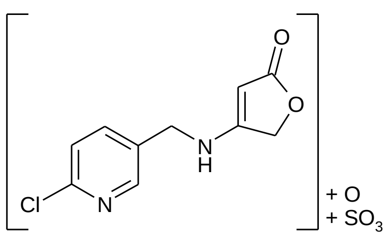
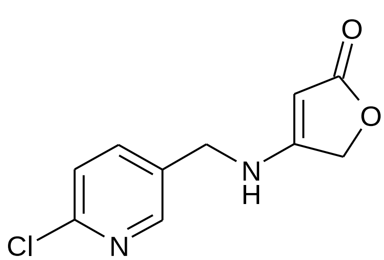
	CRC Turnip root (135d)		2.0P (0.001)
BYI CHMP di-glyc	Tomato	37P (0.048)	
	Potato		4.4P (0.003)
BYI 02960 CHMP glyc di-SA **And** **BYI 02960 CHMP glyc tri-SA**  Or trisulfate	CRC Swiss chard (29-296d)		3.2-5.3P (0.02-0.08)
6-CNA[4] **6-chloronicotinic acid (IUPAC)** **CAS-No.: 5326-23-8** 	Tomato[2]	13.2P (0.017)	
	Potato[3]	22P (0.016)	
	Apple		1.5P (0.008)
	Cotton		0.4P (0.031)
	Rice		3.1P (0.019)
	CRC Wheat grain		3.8P (0.007)
	CRC Swiss chard		7.0P (0.10)
	CRC Turnip leaf		1.0P (0.008)
	CRC Turnip root		8.5P (0.006)
	Poultry eggs		7.2P (0.006)
	Poultry muscle		8.8P (0.;006)
	Poultry fat		1.8P (<0.001)
	Poultry liver		6.4P (0.028)
	Rat excreta		0.4-6.3 TDA
	Potato		2.3P (0.003)

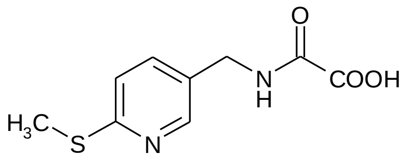
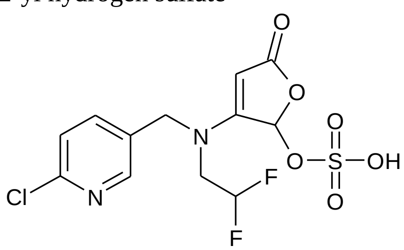
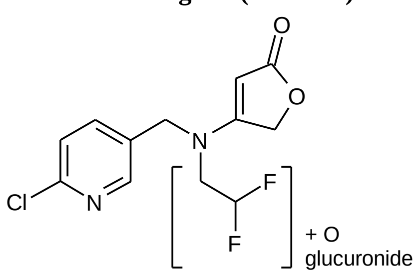
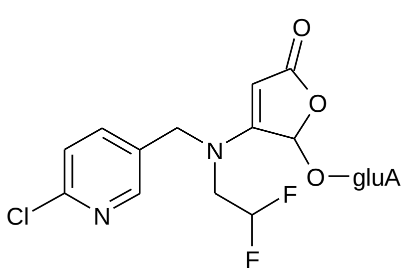
BYI 02960-6-CNA-glycerol-gluA (isomers 1, 2 & 3)  	CRC Wheat grain (14-29% wheat forage, straw, hay)	22P (0.16)	
BYI 02960-difluoroethyl-amino-furanone (DFEAF) 4-[(2,2-difluoroethyl)amino]furan-2(5*H*)-one 	Tomato	10F (0.01)	
	Potato		4.2F (0.003)
	Apple		0.2F (0.003)
	CRC Swiss chard (29d)	17F (0.14)	
	CRC Turnip leaf		1.0F (0.007)
	Rat excreta		0.96-3.5
BYI 02960-difluoroethyl-amino-furanone-OH-glyc  	CRC Swiss chard (29d)		1.2F (0.01)
BYI 02960-AMCP-difluoroethanamine *N*-[(6-chloropyridin-3-yl)methyl]-2,2-difluoroethanamine 	Apple		4.1P (0.023)
	Ruminant liver		1.2P (0.02)
	Ruminant kidney		1.1P (0.02)

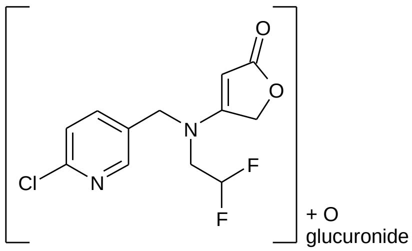
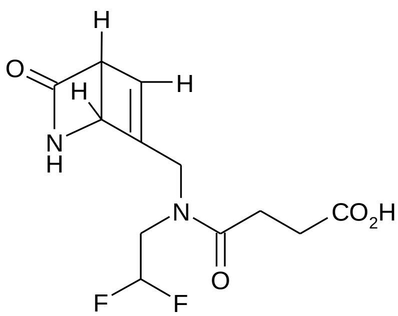
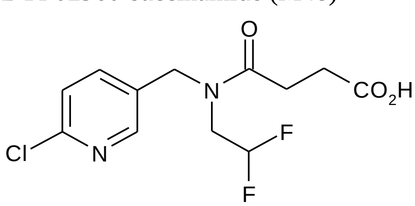
BYI 02960-N-formyl-AMCP-difluoroethanamine *N*-[(6-chloropyridin-3-yl)methyl]-N-(2,2-difluoroethyl)formamide  **And/Or** **BYI 02960-N-acetyl-AMCP-difluoroethanamine** *N*-[(6-chloropyridin-3-yl)methyl]-N-(2,2-difluoroethyl)acetamide  	CRC Swiss chard		2.9P (0.043)
	CRC Turnip leaf		3.6P (0.030)
	CRC Turnip root		3.5P (0.003)
BYI 02960-mercapto-lactic acid 3-({4-[(2,2-difluoroethyl)amino]-2-oxo-2,5-dihydrofuran-3-yl}sulfanyl)-2-hydroxypropanoic acid  	CRC Wheat forage, hay , straw (NOT grain)		1-10F (0.003-0.07)
BYI 02960-amino-furanone 4-aminofuran-2(5*H*)-one	CRC Wheat grain		0.5F (0.002)
	CRC Swiss chard		3.1F (0.02)

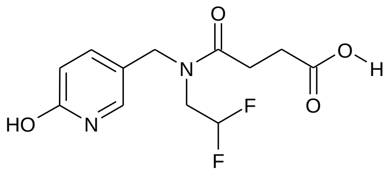
	CRC Turnip leaf		0.9F (0.006)
	CRC Turnip root		4.1 ,(0.003)
BYI 02960-bromo-amino-furanone 4-amino-3-bromofuran-2(5*H*)-one 	CRC Wheat Forage, Straw, Hay (NOT grain)		2-10F (0.01-0.22)
DFA difluoroacetic acid (IUPAC) Acetic acid, 2,2-difluoro- (CAS) CAS-No.: 381-73-7 	Tomato	87 (0.18)	
	Rice* Potato* Cotton* Apple* CRC Wheat* CRC Turnip* CRC Swiss chard* Ruminant* Poultry*		
	*Shown to be present in significant amounts by analysis for non-labeled compound in the metabolism studies and by analyses of crop field trial studies commodity samples and livestock feeding studies commodity samples.		
	Rat excreta		5.3 urine TDA 0.49 feces TDA
Glucose (hexose) 	Tomato	28F (0.026)	
	Apple	14F (0.18)	
	Rice		3.6F (0.023)
	CRC Wheat grain	71F (0.34)	
	CRC Turnip root		3.4F (0.003)
ANIMAL METABOLITES ONLY			
Lactose	Ruminant milk	67F (0.70)	

			
BYI 02960-acetyl-AMCP 	Poultry eggs	23P (0.019)	
	Poultry muscle	40P (0.028)	
	Poultry fat	28P (0.006)	
	Poultry liver		6.3P (0.027)
BYI 02960-AMCP-difluoroethanamine-SA 	Poultry liver		0.3P (0.001)
BYI 02960-acetyl-cysteinyl-nicotinic acid 	Poultry liver		0.3P (0.001)
BYI 02960-cysteinyl-nicotinic acid 6-[(2-amino-2-carboxyethyl)sulfanyl]nicotinic acid	Ruminant liver		4.8P (0.058)
	Ruminant kidney		6.1P (0.11)

			
BYI 02960-hippuric acid N-[(6-chloropyridin-3-yl)carbonyl]glycine 	Ruminant milk		9.1P (0.017)
	Ruminant muscle		1.3P (0.005)
	Ruminant kidney		9.5P (0.18)
	Ruminant liver		0.8 (0.01)
	Rat excreta	1.1 – 10.5 TDA	
BYI 02960-CHMP-serinate 	Poultry excreta	-	-
BYI 02960-des-difluoroethyl-OH-SA 	Poultry muscle		2.1P (0.001) 0.5F (0.001)
	Poultry fat		5.6P (0.001)
	Poultry liver		3.1P (0.014) 0.2F (0.004)
	Poultry eggs		0.1F (0.001)
BYI 02960-des-difluoroethyl 4-[(6-chloropyridin-3-ylmethyl)amino]furan-2(5*H*)-one 	Poultry eggs		8.9P (0.007) 1.2F (0.006)
	Poultry muscle		9.9P (0.007) 2.6F (0.005)
	Poultry fat		5.0P (0.001)
	Poultry liver		1.8P (0.008) 0.8F (0.017)
	Ruminant kidney		1.3F (0.019)

	Rat excreta		1.7- 3.4 TDA
BYI 02960-methylthio-glyoxylic acid ({[6-(methylsulfanyl)pyridin-3-yl]methyl}amino)(oxo)acetic acid 	Ruminant milk		1.5P (0.003)
	Ruminant muscle		1.3P (0.005)
BYI 02960-OH-SA 3-{[(6-chloropyridin-3-yl)methyl](2,2-difluoroethyl)amino}-5-oxo-2,5-dihydrofuran-2-yl hydrogen sulfate 	Poultry eggs		5.1P (0.004) 0.6F (0.003)
	Poultry muscle		1.8P (0.00)
	Poultry fat	16P (0.003)	
	Poultry liver	22P (0.098)	5.1F (0.11)
	Rat excreta		0.2 – 0.5 TDA
BYI 02960-OH-gluA (isomer 4) 	Ruminant kidney		7.5P (0.14) 3.5F (0.052)
BYI 02960-OH-gluA (isomer 3); (isomer2) 3-{[(6-chloropyridin-3-yl) methyl](2,2-difluoroethyl) amino}-5-oxo-2,5-dihydrofuran-2-yl beta-D-glucopyranosiduronic acid 	Ruminant kidney	18P (0.33)	6.9F (0.10)
	Ruminant liver		1.4P (0.016)
	Rat excreta		0.4 – 2.4 TDA
BYI 02960-OH-gluA (isomer 1)	Ruminant kidney		6.0P (0.11) 2.2F (0.03)
	Rat excreta		0.5 – 1.8 TDA

			
Environment Metabolites Only			
BYI 02960-azabicyclosuccinamide (M47)  4-{(2,2-difluoroethyl)[(3-oxo-2-azabicyclo[2.2.0]hex-5-en-6-yl)methyl]amino}-4-oxobutanoic acid		water – aquatic photolysis (major)	
BYI 02960-succinamide (M48)  4-{[(6-chloropyridin-3-yl)methyl](2,2-difluoroethyl)amino}-4-oxobutanoic acid		water – aquatic photolysis (major)	

BYI 02960-deschlorohydroxysuccinamide (M49)  4-{(2,2-difluoroethyl)[(6-hydroxypyridin-3-yl)methyl]amino}-4-oxobutanoic acid			water – aquatic photolysis (minor)
Tomato: 0.535 lb ai/acre soil drench, 1.5X, at first bud, 69 - 73 day PHI. Potato: 0.25 lb ai/acre seed piece treatment. No label except soybean seed treatment. Apple: 0.155 lb ai/acre foliar, 0.42 X, 14 day PHI Cotton: 0.344 lb ai/acre foliar, 0.94X, 90% bolls open Paddy Rice 1: 0.38 lb ai/acre as GR to soil at transplant Paddy Rice 2: 0.37 lb ai/acre foliar to rice plants, 30 day PHI. No label, but 1X numerous other crop foliar uses. Hen: 1.0 mg ai/kg bw X 14 days, or 16 -17 mg ai/kg feed/day Goat: 1.0 mg ai/kg bw X 5 days, or 24 mg ai/kg feed/day Rat: 2 mg/kg bw and 200 mg/kg bw. Confined Rotational: 0.387 lb ai/acre to soil (1.1X)			

Appendix D. Review of Human Research

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These data, which include Pesticide Handlers Exposure Database Version 1.1 (PHED 1.1); the Agricultural Handler Exposure Task Force (AHETF) database; and ExpoSAC Policy 14 and 15.1 (SOPs for Seed Treatment), are (1) subject to ethics review pursuant to 40 CFR 26, (2) have received that review, and (3) are compliant with applicable ethics requirements. For certain studies, the ethics review may have included review by the Human Studies Review Board. Descriptions of data sources, as well as guidance on their use, can be found at the Agency website[6].

[6] http://www.epa.gov/pesticides/science/handler-exposure-data.html and http://www.epa.gov/pesticides/science/post-app-exposure-data.html

Appendix E. Qualitative Evaluation of DFA

Studies submitted in support of the registration of flupyradifurone indicate that there could be significant exposure to difluoroacetic acid (DFA) in drinking water and in food (plants and animals); DFA was shown to be a mammalian metabolite with approximately 6% of flupyradifurone administered to rats being converted to DFA.

Hazard Considerations

The most sensitive flupyradifurone effects seen in the database were skeletal muscle myofiber atrophy/degeneration, decreases in body weight, and decreases in body weight gain at the LOAEL of 33 mg/kg/day in the 90-day dog oral toxicity study (NOAEL = 12 mg/kg/day). However, these effects would not be expected from DFA, which has a very different chemical structure. DFA is also much more polar than the parent compound, which may indicate it can be excreted more rapidly.

The Registrant submitted a genotoxicity study, a range-finding rat toxicity (14-day) study, and a sub-chronic rat (90-day) toxicity study with DFA. DFA produced black foci in the glandular part of the stomach with correlated histopathology findings of focal glandular erosion/necrosis at 66.2/78.8 mg/kg/day (M/F). These dose levels and effects confirm that DFA and flupyradifurone produce different effects on target different tissues. Although these effects occurred at similar potencies (similar comparable NOAELs and LOAELs on a molar basis[7]), the effects are different. Therefore, the toxicity to DFA should be evaluated separately from flupyradifurone. DFA was found in tissues (up to 50%) when flupyradifurone was administered to rats in the subchronic toxicity studies, so the toxicity of DFA has already been considered somewhat in the flupyradifurone toxicity studies and risk assessment. A qualitative Structure-Activity Relationship Analysis using DEREK Nexus 2.0 did not identify any toxicity endpoints of concern and the structure of DFA does not cause any specific toxicity concerns. One study in the literature identified kidney toxicity when administered intra-peritoneally at doses approximately 10X the NOAEL. However, kidney toxicity was not observed in the sub-chronic rat (dietary) toxicity study at doses up to 380 mg/kg/day.

Therefore, although flupyradifurone and DFA produce toxicity at similar dose levels, the effects are not the same, so parent and metabolite cannot be evaluated together. There are no additional toxicity concerns based on DFA’s chemical structure or based on any additional literature studies.

Exposure Considerations

Exposure to DFA as a result of flupyradifurone application is expected in food (plant- and animal- based) and drinking water. DFA was not a major metabolite in most plant commodities,

---

[7] Calculation of Equivalent Dose Between DFA and the Parent Compound: MW flupyradifurone = 289 g/mol MW DFA = 97 g/mol. 289 g/mol ÷ 97 g/mol = ~ 3 g/mol. NOAEL in 90 day rat oral toxicity study with flupyradifurone = 30/38 (M/F) mg/kg/day. NOAEL in 14 day rat oral toxicity study with DFA = 12.7/15.6 (M/F) mg/kg/day. 30 mg/kg/day ÷ 3 = ~10 mg/kg/day (which is similar on a molar basis to the DFA NOAEL of 12.7 mg/kg/day.

but was very significant for the following uses: seed treatment (soybean), soil drench (tomato), and foliar (succulent legume vegetables, especially green beans and lima beans, and cucurbits). DFA was a major degradate on a relative basis in poultry commodities; but on an absolute basis, only very small concentrations of DFA and parent are anticipated at the calculated livestock feeding (exposure) levels. DFA is a major environmental degradate depending upon the soil type and environmental conditions. DFA is expected to be more mobile than the parent compound. Therefore, exposure to DFA is still expected to be relatively low compared to exposure to parent flupyradifurone.

The Agency conducted an exposure assessment using conservative drinking water estimates (see table below) and residue data from crop field trials. (The inputs are presented at the end of this appendix.) When conducting a screening evaluation of DFA, exposure to DFA is 7X less than estimated exposure to flupyradifurone for the general US population, and 5X less than estimated exposure to flupyradifurone for children 1-2 years old, the highest exposed population subgroup.

Table E. Tier I EDWCs for residues of Difluoroacetic acid (DFA).[1]

Source of Drinking Water (Model)	**DFA concentration in drinking water (µg/L)**	
	Acute	**Annual Average or Post Breakthrough Average**
Surface Water (Modified Tier 1 Rice Model)	43	43
Surface water (PRZM/EXAMS)	7.35 (1 season) 8.18 (2 seasons) 9.71 (3 seasons)	4.34 (1 season) 5.12 (2 seasons) 7.74 (3 seasons)
Groundwater (PRZM-GW)	51.7 (1 season) 105 (2 seasons) 152 (3 seasons)	36.0 (1 season) 76.2 (2 seasons) **114** (3 seasons)

[1] Refinements can be made to get lower EDWCs. Tier II modeling could be conducted to determine EDWC in groundwater.

Exposure Considerations

While DFA produces toxicity at a similar potency to the parent compound (similar NOAELs and LOAELs on a molar basis), DFA has already been evaluated somewhat in available subchronic toxicity studies; is polar and likely to be excreted more rapidly than the parent compound in mammals; and its chemical structure does not trigger any specific toxicity concerns. Additionally, a screening evaluation of exposure to DFA showed at least 5X less exposure to DFA than to flupyradifurone using conservative screening evaluation inputs (noted below). Since there is similar potency (albeit with different toxic effects) between flupyradifurone and DFA, and a highly conservative assessment indicates exposure to DFA is at least five times less than the parent compound, the Agency has no additional risk concerns about exposure to DFA.

Inputs for the Screening Evaluation of DFA

The chronic dietary exposure analysis of flupyradifurone is conservative, incorporating recommended tolerance-level values, conservative processing factors based on empirical data, and drinking water estimates that assume 3 growing seasons per year. The assessment also assumed that 100% of the proposed crops were treated with flupyradifurone.

```
U.S. EPA                                                Ver. 3.16, 03-08-d
DEEM-FCID Chronic analysis for DFA - FLUPYRADIFURONE METABOLITE
                                                           NHANES 2003-2008 2-day
Residue file name: C:\Users\KRURY\Documents\My Work Files\BYI
02960\Dietary\DFAEstimateMedian of Highest Rep Crops with individual Medians and 10X
without cranberry.R08
                                                  Adjustment factor #2 NOT used.
Analysis Date 07-15-2014/13:11:53     Residue file dated: 07-15-2014/13:11:29
Reference dose (RfD, Chronic) = .0127 mg/kg bw/day
===============================================================================
                    Total exposure by population subgroup
-------------------------------------------------------------------------------
```

Population Subgroup	Total Exposure: mg/kg body wt/day	Total Exposure: Percent of Rfd
Total US Population	0.003989	31.4%
Hispanic	0.004098	32.3%
Non-Hisp-White	0.004037	31.8%
Non-Hisp-Black	0.003395	26.7%
Non-Hisp-Other	0.004485	35.3%
Nursing Infants	0.003389	26.7%
Non-Nursing Infants	0.011014	86.7%
Female 13+ PREG	0.003566	28.1%
Children 1-6	0.008134	64.0%
Children 7-12	0.004445	35.0%
Male 13-19	0.003185	25.1%
Female 13-19/NP	0.003068	24.2%
Male 20+	0.003411	26.9%
Female 20+/NP	0.003560	28.0%
Seniors 55+	0.003372	26.6%
All Infants	0.008660	68.2%
Female 13-50	0.003482	27.4%
Children 1-2	0.010061	79.2%
Children 3-5	0.007325	57.7%
Children 6-12	0.004730	37.2%
Youth 13-19	0.003125	24.6%
Adults 20-49	0.003543	27.9%
Adults 50-99	0.003418	26.9%
Female 13-49	0.003484	27.4%

Appendix F. Occupational Exposure Tables

Table F.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Flupyradifurone with Baseline Attire.

Exposure Scenario	Crop or Target	Level of Concern	Dermal Unit Exposure (µg/lb ai)[1]	Inhalation Unit Exposure (µg/lb ai)[1]	Maximum Application Rate[2]	Area Treated or Amount Handled Daily[3]	Dermal		Inhalation		Total
			Baseline	Baseline			Dose (mg/kg/day)[4]	MOE[5]	Dose (mg/kg/day)[6]	MOE[7]	MOE[8]
Mixer/Loader											
Mixing/Loading Liquids for Aerial Application	Crop Group 10-10 (Citrus), Crop Group 11-10 (Pome Fruit), Crop Group 13-07B (Bushberries, Highbush), Crop Group 14 (Tree Nuts, Except Almonds)	100	220	0.219	0.18 lb ai/A	350 acres	0.0129	930	0.000173	69,000	920
	Hops	100	220	0.219	0.14 lb ai/A	350 acres	0.010	1,200	0.000134	90,000	1,200
	Field crop, typical[9]	100	220	0.219	0.18 lb ai/A	350 acres	0.0129	930	0.000173	69,000	920
	Crop Group 15 (Cereal Grains), Cotton, Crop Group 18 (Alfalfa & Forage Crops), Peanuts, Crop Subgroup 1C, Crop Group 6 (Legume Vegetables)	100	220	0.219	0.18 lb ai/A	1200 acres	0.0441	270	0.000591	20,000	270
Mixing/Loading for Airblast Application	Crop Group 10-10 (Citrus), Crop Group 11-10 (Pome Fruit), Crop Group 13-07B (Bushberries, Highbush), Crop Group 14 (Tree Nuts, Except Almonds)	100	220	0.219	0.18 lb ai/A	40 acres	0.00147	8,200	0.0000198	610,000	8,100
	Hops	100	220	0.219	0.14 lb ai/A	40 acres	0.00114	11,000	0.0000154	780,000	11,000
Mixing/Loading for Chemigation Application	Soil Directed: Crop Group 10-10 (Citrus), Crop Group 11-10 (Pome Fruit), Crop Group 13-07B (Bushberries, Highbush), Crop Group 14 (Tree Nuts, Except Almonds)	100	220	0.219	0.365 lb ai/A	350 acres	0.0261	460	0.000350	34,000	450

Table F.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Flupyradifurone with Baseline Attire.											
Exposure Scenario	**Crop or Target**	**Level of Concern**	**Dermal Unit Exposure (µg/lb ai)[1]**	**Inhalation Unit Exposure (µg/lb ai)[1]**	**Maximum Application Rate[2]**	**Area Treated or Amount Handled Daily[3]**	**Dermal**		**Inhalation**		**Total**
			Baseline	**Baseline**			**Dose (mg/kg/day)[4]**	**MOE[5]**	**Dose (mg/kg/day)[6]**	**MOE[7]**	**MOE[8]**
	Broadcast: Field crop, typical[9]	100	220	0.219	0.18 lb ai/A	350 acres	0.0129	930	0.000173	69,000	920
	Soil Directed: Field Crop Typical[9]	100	220	0.219	0.365 lb ai/A	350 acres	0.0261	460	0.000350	34,000	450
	Broadcast: Crop Group 15 (Cereal Grains), Cotton, Crop Group 18 (Alfalfa & Forage Crops), Peanuts, Crop Subgroup 1C, Crop Group 6 (Legume Vegetables)	100	220	0.219	0.18 lb ai/A	350 acres	0.0129	930	0.000173	69,000	920
Mixing/Loading for Groundboom Application	Broadcast: Field Crop Typical[9]	100	220	0.219	0.18 lb ai/A	80 acres	0.00294	4,100	0.0000394	300,000	4,000
	Soil Directed: Field Crop Typical[9]	100	220	0.219	0.365 lb ai/A	80 acres	0.00595	2,000	0.0000799	150,000	2,000
	Broadcast: Crop Group 15 (Cereal Grains), Cotton, Crop Group 18 (Alfalfa & Forage Crops), Peanuts, Crop Subgroup 1C, Crop Group 6 (Legume Vegetables)	100	220	0.219	0.18 lb ai/A	200 acres	0.00735	1,600	0.0000985	120,000	1,600
Applicator											
Aerial Application	Crop Group 10-10 (Citrus), Crop Group 11-10 (Pome Fruit), Crop Group 13-07B (Bushberries, Highbush), Crop Group 14 (Tree Nuts, Except Almonds)	100	2.08	0.0049	0.18 lb ai/A	350 acres	0.000122	98,000	0.00000386	3,100,000	95,000
	Hops	100	2.08	0.0049	0.14 lb ai/A	350 acres	0.0000946	130,000	0.0000030	4,000,000	130,000
	Broadcast: Field crop, typical[9]	100	2.08	0.0049	0.18 lb ai/A	350 acres	0.000122	98,000	0.00000386	3,100,000	95,000

Table F.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Flupyradifurone with Baseline Attire.											
Exposure Scenario	**Crop or Target**	**Level of Concern**	**Dermal Unit Exposure (µg/lb ai)[1]**	**Inhalation Unit Exposure (µg/lb ai)[1]**	**Maximum Application Rate[2]**	**Area Treated or Amount Handled Daily[3]**	**Dermal**		**Inhalation**		**Total**
			Baseline	**Baseline**			**Dose (mg/kg/day)[4]**	**MOE[5]**	**Dose (mg/kg/day)[6]**	**MOE[7]**	**MOE[8]**
	Crop Group 15 (Cereal Grains), Cotton, Crop Group 18 (Alfalfa & Forage Crops), Peanuts, Crop Subgroup 1C, Crop Group 6 (Legume Vegetables)	100	2.08	0.0049	0.18 lb ai/A	1200 acres	0.000416	29,000	0.0000133	900,000	28,000
Airblast Application	Crop Group 10-10 (Citrus), Crop Group 11-10 (Pome Fruit), Crop Group 13-07B (Bushberries, Highbush), Crop Group 14 (Tree Nuts, Except Almonds)	100	1,770	4.71	0.18 lb ai/A	40 acres	0.0118	1,000	0.000424	28,000	970
	Hops	100	1,770	4.71	0.14 lb ai/A	40 acres	0.00919	1,300	0.00033	36,000	1,300
Groundboom Application	Broadcast: Field crop, typical[9]	100	78.6	0.34	0.18 lb ai/A	80 acres	0.00105	11,000	0.0000613	200,000	10,000
	Soil Directed: Field crop, typical[9]	100	78.6	0.34	0.365 lb ai/A	80 acres	0.00213	5,600	0.000124	97,000	5,300
	Crop Group 15 (Cereal Grains), Cotton, Crop Group 18 (Alfalfa & Forage Crops), Peanuts, Crop Subgroup 1C, Crop Group 6 (Legume Vegetables)	100	78.6	0.34	0.18 lb ai/A	200 acres	0.00262	4,600	0.000153	78,000	4,300
Flagger											
Flagger for Aerial	Hops	100	11	0.35	0.14 lb ai/A	350 acres	0.00050	24,000	0.000215	56,000	17,000

Table F.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Flupyradifurone with Baseline Attire.											
Exposure Scenario	Crop or Target	Level of Concern	Dermal Unit Exposure (µg/lb ai)[1]	Inhalation Unit Exposure (µg/lb ai)[1]	Maximum Application Rate[2]	Area Treated or Amount Handled Daily[3]	Dermal		Inhalation		Total
			Baseline	Baseline			Dose (mg/kg/day)[4]	MOE[5]	Dose (mg/kg/day)[6]	MOE[7]	MOE[8]
Application	Crop Group 10-10 (Citrus), Crop Group 11-10 (Pome Fruit), Crop Group 13-07B (Bushberries, Highbush), Crop Group 14 (Tree Nuts, Except Almonds), Field crop, typical[9], Crop Group 15 (Cereal Grains), Cotton, Crop Group 18 (Alfalfa & Forage Crops), Peanuts, Crop Subgroup 1C, Crop Group 6 (Legume Vegetables)	100	11	0.35	0.18 lb ai/A	350 acres	0.00643	19,000	0.000276	43,000	13,000
Mixer/loader/Applicator											
Backpack Sprayer	Ground/Soil Directed: Crop Group 10-10 (Citrus)	100	8,260	2.58	0.0365 lb ai/gal	40 gallons	0.0112	1,100	0.0000471	250,000	1,100
Mechanically Pressurized Handgun	Broadcast: Crop Group 10-10 (Citrus), Crop Group 11-10 (Pome Fruit), Crop Group 13-07B (Bushberries, Highbush), Crop Group 14 (Tree Nuts, Except Almonds)	100	1,300	3.9	0.0365 lb ai/gal	1,000 gallons	0.0441	270	0.00178	6,700	260
	Ground/Soil Directed: Crop Group 10-10 (Citrus)	100	1,300	3.9	0.0365 lb ai/gal	1,000 gallons	0.0441	270	0.00178	6,700	260
	Broadcast: Field crop, typical[9]	100	1,300	3.9	0.0365 lb ai/gal	1,000 gallons	0.0441	270	0.00178	6,700	260
	Soil Application: Field crop, typical[9]	100	1,300	3.9	0.0365 lb ai/gal	1,000 gallons	0.0441	270	0.00178	6,700	260

1 Based on the “Occupational Pesticide Handler Unit Exposure Surrogate Reference Table” (May 2013); Level of mitigation: Baseline. *Aerial Application is assessed assuming a closed cockpit (engineering controls).
2 Based on proposed label (Reg. No. Sivanto™ (EPA Reg. No. 264-RRUR)).
3 Exposure Science Advisory Council Policy #9.1.

4 Dermal Dose = Dermal Unit Exposure (μg/lb ai) × Conversion Factor (0.001 mg/μg) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled (A or gal/day) × DAF (7.42%) ÷ BW (80 kg).
5 Dermal MOE = Dermal NOAEL (mg/kg/day) ÷ Dermal Dose (mg/kg/day).
6 Inhalation Dose = Inhalation Unit Exposure (μg/lb ai) × Conversion Factor (0.001 mg/μg) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled (A or gal/day) ÷ BW (80 kg).
7 Inhalation MOE = Inhalation NOAEL (mg/kg/day) ÷ Inhalation Dose (mg/kg/day).
8 Total MOE = NOAEL (12 mg/kg/day) ÷ (Dermal Dose + Inhalation Dose).
9 Crop Subgroup 1B (except sugarbeet), Crop Group 4 (Leafy Vegetables, except *Brassica*), Crop Group 5 (*Brassica* Cole Leafy Vegetables), Foliar Application to Crop Group 8-10 (Fruiting Vegetables), Foliar Application Crop Group 9 (Cucurbit Vegetables), Crop Group 13-07B (Bushberries, lowbush), Crop Subgroup 13-07G (Low Growing Berries).

Table F.2. Occupational Handler Non-Cancer Exposure and Risk Estimates for Flupyradifurone with Label-Specified PPE (Gloves).

Exposure Scenario	Crop or Target	Level of Concern	Dermal Unit Exposure (μg/lb ai)[1]	Inhalation Unit Exposure (μg/lb ai)[1]	Maximum Application Rate[2]	Area Treated or Amount Handled Daily[3]	Dermal		Inhalation		Total
			Gloves	Baseline			Dose (mg/kg/day)[4]	MOE[5]	Dose (mg/kg/day)[6]	MOE[7]	MOE[8]
Mixer/Loader											
Mixing/Loading Liquids for Aerial Application	Crop Group 10-10 (Citrus), Crop Group 11-10 (Pome Fruit), Crop Group 13-07B (Bushberries, Highbush), Crop Group 14 (Tree Nuts, Except Almonds)	100	37.6	0.219	0.18 lb ai/A	350 acres	0.0022	5,500	0.000173	69,000	5,100
	Hops	100	37.6	0.219	0.14 lb ai/A	350 acres	0.00177	7,000	0.000134	90,000	6,500
	Field crop, typical[9]	100	37.6	0.219	0.18 lb ai/A	350 acres	0.00220	5,500	0.000173	69,000	5,100
	Crop Group 15 (Cereal Grains), Cotton, Crop Group 18 (Alfalfa & Forage Crops), Peanuts, Crop Subgroup 1C, Crop Group 6 (Legume Vegetables)	100	37.6	0.219	0.18 lb ai/A	1200 acres	0.00753	1,600	0.000591	20,000	1,500
Mixing/Loading for Airblast Application	Crop Group 10-10 (Citrus), Crop Group 11-10 (Pome Fruit), Crop Group 13-07B (Bushberries, Highbush), Crop Group 14 (Tree Nuts, Except Almonds)	100	37.6	0.219	0.18 lb ai/A	40 acres	0.000251	48,000	0.0000198	610,000	44,000
	Hops	100	37.6	0.219	0.14 lb ai/A	40 acres	0.000196	61,000	0.0000154	780,000	57,000
Mixing/Loading for Chemigation	Soil Directed: Crop Group 10-10 (Citrus),	100	37.6	0.219	0.365 lb ai/A	350 acres	0.00445	2,700	0.000350	34,000	2,500

Table F.2. Occupational Handler Non-Cancer Exposure and Risk Estimates for Flupyradifurone with Label-Specified PPE (Gloves).											
Exposure Scenario	Crop or Target	Level of Concern	Dermal Unit Exposure (µg/lb ai)[1]	Inhalation Unit Exposure (µg/lb ai)[1]	Maximum Application Rate[2]	Area Treated or Amount Handled Daily[3]	Dermal		Inhalation		Total
			Gloves	Baseline			Dose (mg/kg/day)[4]	MOE[5]	Dose (mg/kg/day)[6]	MOE[7]	MOE[8]
Application	Crop Group 11-10 (Pome Fruit), Crop Group 13-07B (Bushberries, Highbush), Crop Group 14 (Tree Nuts, Except Almonds)										
	Broadcast: Field crop, typical[9]	100	37.6	0.219	0.18 lb ai/A	350 acres	0.00220	5,500	0.000173	69,000	5,100
	Soil Directed: Field Crop Typical[9]	100	37.6	0.219	0.365 lb ai/A	350 acres	0.00445	2,700	0.000350	34,000	2,500
	Broadcast: Crop Group 15 (Cereal Grains), Cotton, Crop Group 18 (Alfalfa & Forage Crops), Peanuts, Crop Subgroup 1C, Crop Group 6 (Legume Vegetables)	100	37.6	0.219	0.18 lb ai/A	350 acres	0.00220	5,500	0.000173	69,000	5,100
Mixing/Loading for Groundboom Application	Broadcast: Field Crop Typical[9]	100	37.6	0.219	0.18 lb ai/A	80 acres	0.000502	24,000	0.0000394	300,000	22,000
	Soil Directed: Field Crop Typical[9]	100	37.6	0.219	0.365 lb ai/A	80 acres	0.00102	12,000	0.0000799	150,000	11,000
	Broadcast: Crop Group 15 (Cereal Grains), Cotton, Crop Group 18 (Alfalfa & Forage Crops), Peanuts, Crop Subgroup 1C, Crop Group 6 (Legume Vegetables)	100	37.6	0.219	0.18 lb ai/A	200 acres	0.00125	9,600	0.0000985	120,000	8,900
Applicator											
Aerial Application	Crop Group 10-10 (Citrus), Crop Group 11-10 (Pome Fruit), Crop Group 13-07B (Bushberries, Highbush), Crop Group 14 (Tree Nuts,	100	2.08	0.0049	0.18 lb ai/A	350 acres	0.000122	98,000	0.00000386	3,100,000	95,000

Table F.2. Occupational Handler Non-Cancer Exposure and Risk Estimates for Flupyradifurone with Label-Specified PPE (Gloves).											
Exposure Scenario	Crop or Target	Level of Concern	Dermal Unit Exposure (µg/lb ai)[1]	Inhalation Unit Exposure (µg/lb ai)[1]	Maximum Application Rate[2]	Area Treated or Amount Handled Daily[3]	Dermal		Inhalation		Total
			Gloves	Baseline			Dose (mg/kg/day)[4]	MOE[5]	Dose (mg/kg/day)[6]	MOE[7]	MOE[8]
	Except Almonds)										
	Hops	100	2.08	0.0049	0.14 lb ai/A	350 acres	0.0000946	130,000	0.0000030	4,000,000	130,000
	Broadcast: Field crop, typical[9]	100	2.08	0.0049	0.18 lb ai/A	350 acres	0.000122	98,000	0.00000386	3,100,000	95,000
	Crop Group 15 (Cereal Grains), Cotton, Crop Group 18 (Alfalfa & Forage Crops), Peanuts, Crop Subgroup 1C, Crop Group 6 (Legume Vegetables)	100	2.08	0.0049	0.18 lb ai/A	1200 acres	0.000416	29,000	0.0000133	900,000	28,000
Airblast Application	Crop Group 10-10 (Citrus), Crop Group 11-10 (Pome Fruit), Crop Group 13-07B (Bushberries, Highbush), Crop Group 14 (Tree Nuts, Except Almonds)	100	1,590	4.71	0.18 lb ai/A	40 acres	0.0106	1,100	0.000424	28,000	1,100
	Hops	100	1,590	4.71	0.14 lb ai/A	40 acres	0.00825	1,500	0.00033	36,000	1,400
Groundboom Application	Broadcast: Field crop, typical[9]	100	16.1	0.34	0.18 lb ai/A	80 acres	0.000215	56,000	0.0000613	200,000	44,000
	Soil Directed: Field crop, typical[9]	100	16.1	0.34	0.365 lb ai/A	80 acres	0.000436	28,000	0.000124	97,000	22,000
	Crop Group 15 (Cereal Grains), Cotton, Crop Group 18 (Alfalfa & Forage Crops), Peanuts, Crop Subgroup 1C, Crop Group 6 (Legume Vegetables)	100	16.1	0.34	0.18 lb ai/A	200 acres	0.000538	22,000	0.000153	78,000	17,000
Flagger											
Flagger for Aerial	Hops	100	12	0.35	0.14 lb ai/A	350 acres	0.000545	22,000	0.000215	56,000	16,000

Table F.2. Occupational Handler Non-Cancer Exposure and Risk Estimates for Flupyradifurone with Label-Specified PPE (Gloves).											
Exposure Scenario	**Crop or Target**	**Level of Concern**	**Dermal Unit Exposure (µg/lb ai)[1]**	**Inhalation Unit Exposure (µg/lb ai)[1]**	**Maximum Application Rate[2]**	**Area Treated or Amount Handled Daily[3]**	**Dermal**		**Inhalation**		**Total**
			Gloves	**Baseline**			**Dose (mg/kg/day)[4]**	**MOE[5]**	**Dose (mg/kg/day)[6]**	**MOE[7]**	**MOE[8]**
Application	Crop Group 10-10 (Citrus), Crop Group 11-10 (Pome Fruit), Crop Group 13-07B (Bushberries, Highbush), Crop Group 14 (Tree Nuts, Except Almonds), Field crop, typical[9], Crop Group 15 (Cereal Grains), Cotton, Crop Group 18 (Alfalfa & Forage Crops), Peanuts, Crop Subgroup 1C, Crop Group 6 (Legume Vegetables)	100	12	0.35	0.18 lb ai/A	350 acres	0.000701	17,000	0.000276	43,000	12,000
Mixer/loader/Applicator											
Backpack Sprayer	Ground/Soil Directed: Crop Group 10-10 (Citrus)	100	8,260	2.58	0.0365 lb ai/gal	40 gallons	0.0112	1,100	0.0000471	250,000	1,100
Mechanically Pressurized Handgun	Broadcast: Crop Group 10-10 (Citrus), Crop Group 11-10 (Pome Fruit), Crop Group 13-07B (Bushberries, Highbush), Crop Group 14 (Tree Nuts, Except Almonds)	100	1,300	3.9	0.0365 lb ai/gal	1,000 gallons	0.0132	910	0.00178	6,700	800
	Ground/Soil Directed: Crop Group 10-10 (Citrus)	100	1,300	3.9	0.0365 lb ai/gal	1,000 gallons	0.0132	910	0.00178	6,700	800
	Broadcast: Field crop, typical[9]	100	1,300	3.9	0.0365 lb ai/gal	1,000 gallons	0.0132	910	0.00178	6,700	800
	Soil Application: Field crop, typical[9]	100	1,300	3.9	0.0365 lb ai/gal	1,000 gallons	0.0132	910	0.00178	6,700	800

1 Based on the "Occupational Pesticide

Handler Unit Exposure Surrogate Reference Table" (May 2013); Level of mitigation: Gloves. *Aerial Application is assessed assuming a closed cockpit (engineering controls).

2 Based on proposed label (Reg. No. Sivanto™ (EPA Reg. No. 264-RRUR)).

3 Exposure Science Advisory Council Policy #9.1.

4 Dermal Dose = Dermal Unit Exposure (μg/lb ai) × Conversion Factor (0.001 mg/μg) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled (A or gal/day) × DAF (7.42%) ÷ BW (80 kg).

5 Dermal MOE = Dermal NOAEL (mg/kg/day) ÷ Dermal Dose (mg/kg/day).

6 Inhalation Dose = Inhalation Unit Exposure (μg/lb ai) × Conversion Factor (0.001 mg/μg) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled (A or gal/day) ÷ BW (80 kg).

7 Inhalation MOE = Inhalation NOAEL (mg/kg/day) ÷ Inhalation Dose (mg/kg/day).

8 Total MOE = NOAEL (12 mg/kg/day) ÷ (Dermal Dose + Inhalation Dose).

9 Crop Subgroup 1B (except sugarbeet), Crop Group 4 (Leafy Vegetables, except *Brassica*), Crop Group 5 (*Brassica* Cole Leafy Vegetables), Foliar Application to Crop Group 8-10 (Fruiting Vegetables), Foliar Application Crop Group 9 (Cucurbit Vegetables), Crop Group 13-07B (Bushberries, lowbush), Crop Subgroup 13-07G (Low Growing Berries).

Table F.3. Summary of Short- and Intermediate-Term Handler Exposures and Risks for Flupyradifurone Seed Treatment of Soybean Seeds[1].								
Maximum Application Rate[2]	Dermal Unit Exposure[3]	Inhalation Unit Exposure[3]	Amount of Seed Treated or Planted Per Day[4]	Dermal Dose[5]	Inhalation Dose[6]	Dermal MOE[7]	Inhalation MOE[8]	Combined MOE[9]
lb ai/lb seed	*mg/lb ai*	*mg/lb ai*	*lb seed/day*	*mg/kg/day*	*mg/kg/day*	*LOC = 100*	*LOC = 100*	*LOC = 100*
Loader/Applicator								
0.00054	0.023	0.00034	281,250	0.00323	0.00000000032	3,700	38,000,000,000	3,700
Sewer								
0.00054	0.0062	0.00023	281,250	0.000873	0.000000000016	14,000	770,000,000,000	14,000
Bagger								
0.00054	0.0091	0.00016	281,250	0.00128	0.000000000023	9,400	510,000,000,000	9,400
Multiple Activities								
0.00054	0.042	0.0016	281,250	0.00591	0.0000000050	2,000	2,400,000,000	2,000
Planters								
0.00054	0.25	0.0034	26,667	0.0033	0.000000035	3,600	340,000,000	3,600

1 Seed treatment rate calculations are based on the following assumptions: Soybean Seeds: 1,500 to 3,600 seeds per lb.
2 Application Rate based on proposed label for flupyradifurone (EPA Reg. No. 264-RRUE).
3 Unit Exposures from HED Exposure Science Advisory Council Policy 14: Standard Operating Procedures for Seed Treatment (baseline inhalation = no respirator).
4 HED default for lb seed treated/planted per day from HED Exposure Science Advisory Council Interim Policy 15.1 and the BEAD memo "Acres Planted Per Day and Seeding Rates of Crops Grown in the United States" (J. Becker, March 2011).
5 Daily Dermal Dose (mg/kg/day) = daily inhalation unit exposure (mg/lb ai) × application rate (lb ai/lb seed) × amount planted (lb seed/day) × dermal absorption factor (7.42%) ÷ body weight (80 kg adult).
6 Daily Inhalation Dose (mg/kg/day) = daily inhalation unit exposure (mg/lb ai) × application rate (lb ai/lb seed) × amount planted (lb seed/day) ÷ body weight (80 kg adult).
7 Dermal MOE = NOAEL (12 mg/kg/day for short- and intermediate-term exposure) ÷ Dermal Dose (mg/kg/day). Level of concern = 100.
8 Inhalation MOE = NOAEL (12 mg/kg/day for short- and intermediate-term exposure) ÷ Inhalation Dose (mg/kg/day). Short-term level of concern = 100.
9 Total MOE = NOAEL (12 mg/kg/day) ÷ (Dermal Dose + Inhalation Dose).

Table F.4. Worst-Case Short- and Intermediate-Term Occupational Post-application Non-Cancer Exposure and Risk Estimates for Flupyradifurone.

Crop/Site	Activities	Application Rate (lb ai/A)	Transfer Coefficient (cm^2/hr)	DFR[1]	Dermal Dose (mg/kg/day)[2]	MOE[3]
Crop Group 1B and Crop Group 1C (Beet, Potato, Turnip)	Hand Set Irrigation	0.18	1900	0.50	0.0071	1,700
Crop Group 4 (Leafy Vegetables Except *Brassica*)	Hand Set Irrigation	0.18	1900	0.50	0.0071	1,700
Crop Group 5 (*Brassica* Leafy Vegetables)	Scouting, Hand Harvesting, Hand Weeding	0.18	4200	0.50	0.0157	760
Crop Group 6 (Legume Vegetables)	Hand Set Irrigation	0.18	1900	0.50	0.0071	1,700
Crop Group 8-10 (Fruiting Vegetables)	Hand Set Irrigation	0.18	1900	0.50	0.0071	1,700
Crop Group 9 (Cucurbit Vegetables)	Hand Harvesting, Mechanically Assisted Harvesting, Training, Turning,	0.18	550	0.50	0.0021	5,800
Crop Group 10-10 (Citrus)	Hand Harvesting	0.18	1400	0.50	0.0052	2,300
Crop Group 11-10 (Pome Fruit)	Thinning Fruit	0.18	3600	0.50	0.0135	890
Crop Subgroup 13-07B (Bushberries, except cranberry)	Hand Harvesting	0.18	1400	0.50	0.0052	2,300
Crop Subgroup 13-07G (Low Growing Berries)	Hand Harvesting	0.18	1100	0.50	0.0041	2,900
Crop Subgroup 13-07F (Small Fruit Vine Climbing, Except Fuzzy Kiwifruit)	Girdling/Turning	0.18	19300	0.50	0723	170
Crop Group 14 (Tree Nuts, Except Almonds)	Hand Harvesting (Net)	0.18	1400	0.50	0.0052	2,300
Crop Group 15 (Cereal Grains, Except Rice)	Detasseling/Hand Harvesting (Sweet Corn Only)	0.18	8800	0.50	0.0330	360
	Hand Set Irrigation	0.18	1900	0.50	0.0071	1,700
Crop Group 18 [Non-Grass Animal Feeds (Forage, Fodder, Straw, Hay)]	Hand Set Irrigation	0.18	1900	0.50	0.0071	1,700
Cotton	Scouting	0.18	210	0.50	0.00079	15,000
Hop	Harvesting, Mechanically Assisted	0.14	19300	0.39	0.0562	210
Peanut	Hand Set Irrigation	0.18	1900	0.50	0.0071	1,700

1 DFR = Application Rate × F × $(1\text{-}D)^t$ × 4.54E8 µg/lb × 2.47E-8 acre/cm^2; where F = 0.25 and D = 0.10 per day

2 Daily Dermal Dose = [DFR (µg/cm^2) × Transfer Coefficient × 0.001 mg/µg × 8 hrs/day × dermal absorption (7.42 %)] ÷ BW (kg).

3 MOE = POD (12 mg/kg/day) / Daily Dermal Dose.